"FORMULATION AND EVALUATION OF MUCOADHESIVE BUCCAL PATCHES OF DIMENHYDRINATE"

A Dissertation submitted to

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY, CHENNAI-32.

In partial fulfillment of the requirements for the award of degree of

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IN PHARMACEUTICS

SUBMITTED BY

REG.NO:26091391

Under the guidance of

Prof.S.P.SENTHIL, M.Pharm., (PhD.,)

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This work is original and has not been submitted in part or full to any other degree or diploma of this or any other university.

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This is to certify that the investigation in this thesis entitled **"FORMULATION AND EVALUATION OF MUCCOADHESIVE BUCCAL PATCHES OF DIMENHYDRINATE"** submitted in partial fulfillment of the requirements for the Degree Of **MASTER OF PHARMACY in PHARMACEUTICS** were carried out in the Pharmaceutics laboratory of The Erode College Of Pharmacy and Research Institute, Erode by **Regd.No.26091391** under the guidance of **Prof. S.P.Senthil, M.Pharm.,(Ph.D.,)** The Erode College Of Pharmacy and Research Institute, Erode.

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DECLARATION

The work presented in this thesis entitled "**FORMULATION AND EVALUATION OF MUCCOADHESIVE BUCCAL PATCHES OF DIMENHYDRINATE"** was carried out by me in the Department of Pharmaceutics, The Erode College of Pharmacy and Research Institute, Erode, under the direct supervision of **Prof. S.P.Senthil M.Pharm., (Ph.D.,), Department of Pharmaceutics, The Erode College of Pharmacy and Research Institute, Erode 638 112.**

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LIST OF ABBRIVIATIONS

1. Abs	Absorbance
2. BM	Basement membrane
3. BP	British Pharmacopoeia
4. CO_2	Carbon dioxide
5. Da	Daltons
6. Fig	Figure
7. FT-IR	Fourier Transform Infrared
8. gm	Gram
9. HEC	Hydroxy ethyl cellulose
10. HPMC	Hydroxy propyl methyl cellulose
11. Hrs	Hours
12. IR	Infrared spectroscopy
13. ICH	International conference of Harmonization
14. L	liter
15. MCG	Membrane Coating Granules
16. mg	Milligram
17. ml	Milliliter
18. NDDS	Novel Drug Delivery System
19. nm	Nanometer
20. PBS	Phosphate buffer saline
21. P^H	Negative logarithm of hydrogen ion concentration
22. PNS	Para sympathetic nervous system
23. PONV	Post operative nausea and vomitng

24. PVA	Polyvinyl alcohol
25. PVP	Polyvinyl pyrolidine
26. RH	Relative humidity
27. RPM	Rotations per minute
28. SEM	Scanning Electron Microscopy
29. SD	Standard deviation
30. SQRT	Square root of time
31. SNS	Sympathetic nervous system
32. USP	United States Pharmacopoeia
33. %	Percentage
34. μm	micro meter

1.1 INTRODUCTION

Oral route has been the commonly adopted and most convenient route for drug delivery. Oral route of administration has been received more attention in the pharmaceutical field because of the more flexibility in the designing of dosage form than drug delivery design for other routes, ease of administration as well as traditional belief that by oral administration the drug is well absorbed as the food stuffs that are ingested daily. Pharmaceutical products designed for oral delivery are mostly the immediate release types which are designed for immediate release of drug for rapid absorption. The term drug delivery covers a very broad range of techniques used to get therapeutic agents in to human body. The limitations of the most obvious and trusted drug delivery techniques those of the ingested tablet and of the intravenous/ intramuscular/ subcutaneous injections have been recognized for some time. The former delivers drug in to the blood only through the hepatic system and hence the amount in the blood stream may be much lower than the amount formulated into the tablet. Further more liver damage is the unfortunate side effect of many soluble tableted drug [3].

To over come some of these limitations, other modes of drug delivery in to the body were investigated. Those are

1. Trans Dermal Drug Delivery System (through the intact skin)
2. Trans Mucosal Drug Delivery System (through the intact mucosa of the mouth, intestine, rectum, vagina or nose)
3. Trans Ocular Drug Delivery System (through the eye)
4. Trans Alveolar Drug Delivery System (inhalation through the lung tissue)

5. Implantable Drug Delivery System (through the subcutaneous and deeper implants, deliver into surrounding tissue)
6. Injectables (I.M or Subcutaneous)

Of the above modes, Transdermal, Transmucosal, Injectables and Subcutaneous Implants have been found varying degree of commercial acceptance [3].

TRANSMUCOSAL DRUG DELIVEY SYSTEM [2]

Delivery of drugs through the absorptive mucosa in various easily accessible body cavities, like the Buccal, ocular, nasal, rectal, and vaginal mucosae, has the advantage of bypassing the hepatic-gastrointestinal first pass elimination associated with oral administration. Further more, because of the dual biophysical and biochemical nature of these mucosal membranes, drugs with hydrophilic and/or hydrophobic characteristics can be readily absorbed.

Different types of transmucosal drug delivery systems are

- Buccal Drug Delivery System.
- Ocular Drug Delivery System.
- Vaginal Drug Delivery System.
- Rectal Drug Delivery System.
- Nasal Drug Delivery System.
- Gastro Intestinal Drug Delivery System.

BUCCAL DRUG DELIVERY SYSTEM [1]

The mucosa of the mouth is very different from the rest of the gastrointestinal tract and morphologically is more similar to skin. Although the permeability of skin is widely regarded as poor, it is not generally appreciated that the oral mucosa lacks the good permeability demonstrated by the intestine. These differences within the gastrointestinal tract can largely be attributed to the organization of the epithelia, which serve very different functions. A simple, single-layered epithelium lines the stomach, small intestine, and colon, which provides for a Minimal transport distance for absorbents. In contrast, a stratified or multilayered epithelium covers the oral cavity and esophagus and, in common with skin, is composed of layers with varying states of differentiation or maturation evident on progression from the basal cell layer to the surface. Drugs have been applied to the oral mucosa for topical applications for many years. However, recently there has been interest in exploiting the oral cavity as a portal for delivering drugs to the systemic circulation. Notwithstanding the relatively poor permeability characteristics of the epithelium, a number of advantages are offered by this route of administration. Foremost among these are the avoidance of first-pass metabolism, ease of access to the delivery site, and the opportunity of sustained drug delivery predominantly via the buccal tissues. Delivery can also be terminated relatively easily if required. The robustness of the epithelium necessary to withstand mastication also serves the drug delivery process well as fast cellular recovery follows local stress and damage. Indeed the two most challenging issues to be addressed in the oral mucosal delivery of drugs are undoubtedly permeability enhancement and dosage form retention at the site of application. The continuous

secretion of saliva and its subsequent swallowing can lead to substantial drug depletion from the dosage form and hence low bioavailability [1].

Advantages [4]

- The oral mucosa has a rich blood supply. Drugs are absorbed from the oral cavity through the oral mucosa, and transported through the deep lingual or facial vein, internal jugular vein and braciocephalic vein into the systemic circulation. Following buccal administration, the drug gains direct entry into the systemic circulation thereby bypassing the first pass effect.
- It is richly vascularized and more accessible for administration and removal of dosage forms.
- No hepatic first-pass effect.
- No pre-systemic metabolism in the gastrointestinal tract.
- Ease of administration
- High patient accessibility.
- An expanse of smooth muscle and relatively immobile mucosa, suitable for administration of retentive dosage forms.
- Bypass exposure of the drugs to the gastrointestinal fluids.
- More rapid cellular recovery and achievement of a localized site on smooth surface of buccal mucosa.
- Low enzyme activity, suitability for drugs/ excipients that mildly and reversibly damages or irritates the mucosa.
- The oral mucosa is routinely exposed to a multitude of different foreign compounds. So it has evolved a robust membrane that is less prone to irreversible damage by drug, dosage form or additives used therein.

- Non-invasive method of drug administration.
- Facility to include permeation enhancer or enzyme inhibitor or pH modifier in the formulation.

Disadvantages

- Low permeability of buccal membrane specifically when compared to the sublingual membrane.
- Small surface area (170 cm2).
- Saliva (0.5–2 L/day) is continuously secreted into the oral cavity diluting drugs at the site of absorption resulting in low drug concentrations at the surface of the absorbing membrane.
- Inconvenience of patient when eating or drinking.

Limitations in buccal absorption

- The area of absorptive membrane is relatively smaller.
- Drugs, which are unstable at buccal pH cannot be administered by this route.
- Only drugs with a small dose requirement can be administered.
- Only those drugs, which are absorbed by passive diffusion, can be administered by this route.
- Eating and drinking may become restricted.
- There is an ever present possibility of the patient swallowing the tablet.
- Over hydration may lead to the formation of slippery surface and structural integrity of the formulation may get disrupted by this swelling and hydration of the buccoadhesive polymers.

ANATOMY AND PHYSIOLOGY OF THE ORAL MUCOSA [5, 6]

Structure

The oral mucosa is anatomically divided into three tissue layers.

These three layers are the 1) epithelium; 2) basement membrane; and 3) connective tissues.

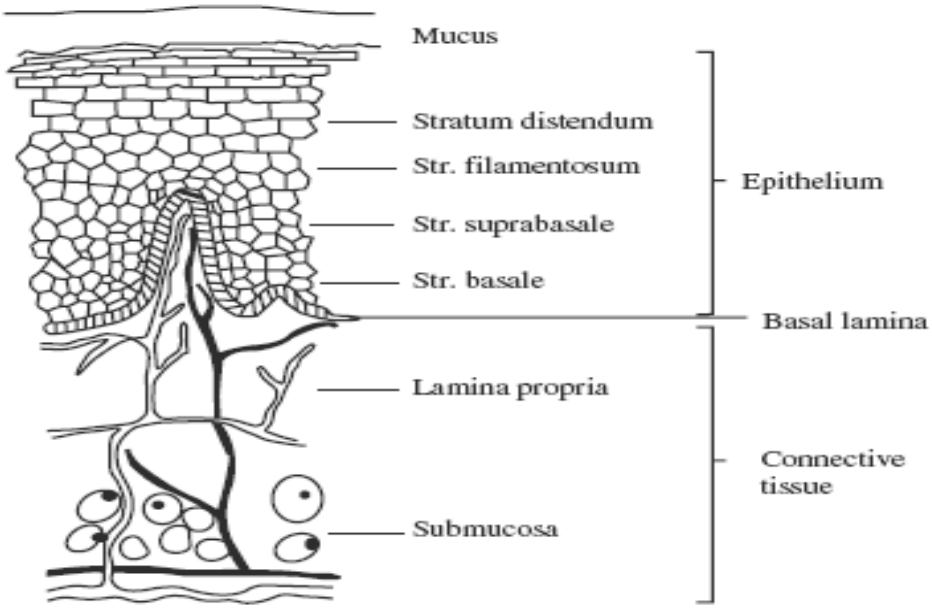


Fig.No.1: Schematic diagram showing the principal components of oral mucosa.

Epithelium

The epithelium consists of approximately 40–50 layers of stratified squamous epithelial cells. The epithelial cells originate from a layer of basal cells, which are cuboidal in shape, undergo continuous mitosis, and move to the surface. As the cells migrate to the surface through the intermediate layers, they differentiate and become larger, flattened, and surrounded by an external lipid matrix (membrane-coating granules). This external lipid matrix determines the drug permeability of the tissue. Although gingiva (gum) and the hard palate are keratinized, areas such as buccal,

sublingual, and the soft palate are non-keratinized. The thickness of buccal epithelium varies with location and typically ranges from 500 to 800 *m*m in humans, dogs, and rabbits. The estimated cell turnover time is 5–6 days. In addition, the buccal epithelium is also characterized by the presence of intercellular gap junctions.

Basement membrane

The basement membrane (BM) is a continuous layer of extracellular materials and forms a boundary between the basal layer of epithelium and the connective tissues of the lamina propria and the sub mucosa. The BM can be subdivided into the a) lamina lucida, b) lamina densa, and c) a sub layer of fibrous material. The functions of the BM include providing

1) Adherence between epithelium and underlying connective tissues

2) Mechanical support for epithelium

3) A barrier to the passage of cells and some large molecules.

Connective tissues

Connective tissues consist of lamina propria and sub mucosa, if present. The lamina propria is a continuous sheet of connective tissue composed of blood capillaries and nerve fibers serving the oral mucosa. Vascular drainage from the oral mucosa is principally by way of the lingual, facial, and retromandibular veins. These veins open into the internal jugular vein and thus avoid first-pass metabolism. The buccal mucosae from monkeys, apes, dogs, pigs, and rabbits possess physiology very similar to that of human buccal mucosa.

Permeability

Permeability barriers

The permeability of buccal mucosa lies somewhat between the skin epidermis and intestinal mucosa. Epithelium the predominant barrier to drug diffusion resides approximately within the outermost one-third of the epithelium. This is true of both keratinized and nonkeratinized epithelia. Therefore, keratinization is unlikely to offer major resistance to buccal permeation. Membrane Coating Granules (MCG), MCGs are spherical or oval organelles (100–300 nm in diameter) found both in keratinized as well as in non-keratinized epithelia but are different with regard to composition in both epithelia. MCGs discharge their contents into the intercellular space and thus form the permeability barrier.

BIOADHESION AND MUCOADHESION [4]

The term bioadhesion can be defined as the state in which two materials, at least one biological in nature, are held together for an extended period of time by interfacial forces, in biological systems, bioadhesion can be classified into 3 types:

- Type 1, adhesion between two biological phases, for example, platelet aggregation and wound healing.
- Type 2, adhesion of a biological phase to an artificial substrate, for example, cell adhesion to culture dishes and biofilm formation on prosthetic devices and inserts.
- Type 3, adhesion of an artificial material to a biological substrate, for example, adhesion of synthetic hydrogels to soft tissues and adhesion of sealants to dental enamel.

For drug delivery purposes, the term bioadhesion implies attachment of a drug carrier system to a specified biological location. The biological surface can be epithelial tissue or the mucus coat on the surface of a tissue. If adhesive attachment is to a mucus coat, the phenomenon is referred to as mucoadhesion. Leung and Robinson described mucoadhesion as the interaction between a mucin surface and a synthetic or natural polymer. Mucoadhesion should not be confused with bioadhesion, in bioadhesion, the polymer is attached to the biological membrane and if the substrate is mucus membrane the term mucoadhesion is used.

THEORIES OF MUCOADHESION [4]:

Various theories exist to explain at least some of the experimental observations made during the bioadhesion process. Unfortunately, each theoretical model can only explain a limited number of the diverse range of interactions that constitute the bioadhesive bond. However, four main theories can be distinguished.

Wetting Theory of Mucoadhesion:

The wetting theory is perhaps the oldest established theory of adhesion. It is best applied to liquid or low-viscosity bioadhesives. It explains adhesion as an embedding process, whereby adhesive agents penetrate into surface irregularities of the substrate and ultimately harden, producing many adhesive anchors. Free movement of the adhesive on the surface of the substrate means that it must overcome any surface tension effects present at the interface. The wetting theory calculates the contact angle and the thermodynamic work of adhesion.

The work done is related to the surface tension of both the adhesive and the substrate, as given by Dupre's equation.

$$\omega_A = \gamma_b + \gamma_t - \gamma_b \qquad \text{------ (1)}$$

Where ω_A is the specific thermodynamic work of adhesion and γ_b, γ_τ, and γ_{bt} represent, respectively, the surface tensions of the bioadhesive polymer, the substrate, and the interfacial tension. The adhesive work done is a sum of the surface tensions of the two adherent phases, less the interfacial tensions apparent between both phases. Horizontal resolution of the forces gives the Young equation:

$$\gamma_{ta} = \gamma_{bt} + \gamma_{ba}\cos\theta \qquad \text{-------- (2)}$$

Where θ is the angle of contact, γ_{bt} is the surface tension between the tissue and polymer, γ_{ba} is the surface tension between polymer and air, and γ_{ta} is the surface tension between tissue and air. Equation 3 states that if the angle of contact, θ is greater than zero, the wetting will be incomplete. If the vector γ_{ta} greatly exceeds γ_{bt} + γ_{ba}, that is:

$$\gamma_{ta} \geq \gamma_{bt} + \gamma_{ba} \qquad \text{-------- (3)}$$

Then θ will approach zero and wetting will be complete. If a bioadhesive material is to successfully adhere to a biological surface, it must first dispel barrier substances and then spontaneously spread across the underlying substrate, either tissue or mucus. The spreading coefficient, S_b, can be defined as shown in Equation 4:

$$S_b = \gamma_{ta} - \gamma_{bt} - \gamma_{ba} > 0 \qquad \text{---------- (4)}$$

This states that bioadhesion is successful if Sb is positive, thereby setting the criteria for the surface tension vectors. In other words, bioadhesion is favored by large values of γ_{ta} or by small values of γ_{bt} and γ_{ba}.

Electrostatic Theory of Mucoadhesion:

According to electrostatic theory, transfer of electrons occurs across the adhesive interface and adhering surface. This results in the establishment of the

electrical double layer at the interface and a series of attractive forces responsible for maintaining contact between the two layers.

Diffusion Theory of Mucoadhesion:

Diffusion theory describes that polymeric chains from the bioadhesive interpenetrate into glycoprotein mucin chains and reach a sufficient depth within the opposite matrix to allow formation of a semi permanent bond. The process can be visualized from the point of initial contact. The existence of concentration gradients will drive the polymer chains of the bioadhesive into the mucus network and the glycoprotein mucin chains into the bioadhesive matrix until an equilibrium penetration depth is achieved.

The exact depth needed for good bioadhesive bonds is unclear, but is estimated to be in the range of 0.2–0.5 μm. The mean diffusional depth of the bioadhesive polymer segments, *s*, may be represented by Equation 5.

$$s = \sqrt{2tD} \qquad \text{---------- (5)}$$

Where *D* is the diffusion coefficient and t is the contact time. Duchene adapted Equation 5 to give Equation 6, which can be used to determine the time, *t*, to bioadhesion of a particular polymer:

$$t = \frac{l^2}{D_b} \qquad \text{---------- (6)}$$

In which *l* represents the interpenetrating depth and D_b the diffusion coefficient of a bioadhesive through the substrate.

Once intimate contact is achieved, the substrate and adhesive chains move along their respective concentration gradients into the opposite phases. Depth of diffusion is dependent on the diffusion coefficient of both phases. Reinhart and Peppas reported that the diffusion coefficient depended on the molecular weight of the polymer strand and that it decreased with increasing cross-linking density.

Adsorption Theory of Mucoadhesion:

According to the adsorption theory, after an initial contact between two surfaces, the materials adhere because of surface forces acting between the chemical structures at the two surfaces. When polar molecules or groups are present, they reorientate at the interface. Chemisorption can occur when adhesion is particularly strong. The theory maintains that adherence to tissue is due to the net result of one or more secondary forces (Vander Waal's forces, hydrogen bonding, and hydrophobic bonding).

Fracture Theory of Adhesion:

This theory describes the force required for the separation of two surfaces after adhesion. The fracture strength is equivalent adhesive strength through the following equation. This theory is useful for the study of bioadhesion by tensile apparatus.

$$\sigma = (E \times \varepsilon/L)^{1/2} \quad \text{---------- (7)}$$

Where σ is the fracture strength, e Fracture energy, E young modulus of elasticity and L the critical crack length.

Measurement of Bioadhesion [5]:

Measurement of bioadhesion not only helps in screening the candidate polymer but also assists in studying the mechanism of bioadhesion. However, performance of the final dosage form containing the polymer and the drug is the best test for bioadhesion.

In vitro measurements:

Measurement of either tensile or shear stress is the most commonly used in vitro method to measure bioadhesion. All in vitro measurements provide a rank order of bioadhesive strength for a series of candidate polymers. Measurement of tensile strength involves quantitating the force required to break the adhesive bond between the test polymer and a model membrane. This method typically uses a modified balance or tensile tester. A section of freshly excised rabbit stomach tissue with the mucosal side exposed is secured on a weighed glass vial and placed in a beaker containing USP-simulated gastric fluid. Another section of the same tissue is secured onto a rubber stopper with a vial cap with the mucus side exposed. A small quantity of the test polymer is placed between the two mucosal tissues. The force required to detach the polymer from the tissue is then recorded. Measurement of shear strength involves quantitating the force that causes the polymer to slide in a direction parallel to the plane of contact between the polymer and the mucus. This method uses a glass plate suspended from a microbalance on which the test polymer is coated. This plate is then dipped in a temperature controlled mucus sample. The force required to pull the plate out of the mucus sample is determined under constant experimental conditions. Additional in vitro methods include adhesion weight, fluorescent probe,

flow channel, mechanical spectroscopic, falling film, colloidal gold staining, viscometric method, thumb test, adhesion number, and electrical conductance.

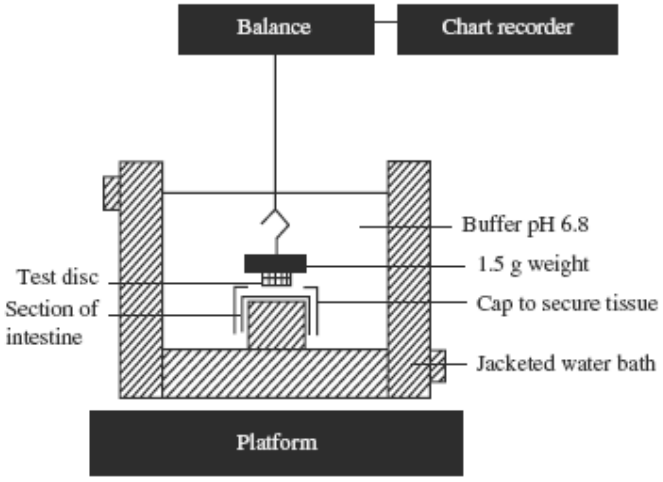


Fig.No.2: The apparatus and the setup for assessing the tensile strength.

In vivo measurements:

In vivo methods are relatively few and measure the residence time of bioadhesives at the application site. Techniques such as *g*-scintigraphy, perfused intestinal loop and radio labeled transit studies using 55Cr-labeled bioadhesive polymer, and 99mTc-labeled polycarbophil have been used for this purpose.

FACTORS AFFECTING SYSTEMIC ORAL MUCOSAL DELIVERY [5]:

Membrane Factors:

Regional differences in both permeability and thickness affect both the rate and extent of drug reaching the systemic circulation. Keratinization and composition, although not major factors, of the various oral mucosae affect systemic mucosal drug delivery. Additional factors such as absorptive membrane thickness, blood supply, blood/lymph drainage, cell renewal rate, and enzyme content will also govern the rate and extent of drug absorption into the systemic circulation.

Environmental Factors:

Saliva:

A major portion of saliva is composed of water (99%) and has a p^H of 6.5–7.5 depending on the flow rate and location. An increase in the salivary flow rate leads to the secretion of watery saliva. Stimulated salivary secretion affects the film thickness and aids in easy migration of test compounds from one region of the mouth to another. Salivary p^H is also important because passive diffusion of unionized drug is the major mechanism of oral absorption.

Salivary glands:

Drug-delivery systems, therefore, should not be placed either over a duct or adjacent to a salivary duct because this may dislodge the retentive system or may result in excessive washout of the drug or rapid dissolution/erosion of the delivery system, making it difficult to achieve high local drug concentrations. Also, if a retentive system is placed over salivary ducts, the reduced salivary flow rate may produce less/no mucus that is required for proper attachment of a mucoadhesive delivery device.

Movement of the oral tissues:

Talking, eating, and swallowing may cause some mouth movement leading to dislodgment of the delivery device. The movement of the tongue may also influence the delivery of drugs from a mucoadhesive, retentive system owing to the tongue swiping across the dosage form and adjacent tissues as well as to induction of suction pressures from the tongue compressing against the hard palate.

Permeant factors [6]:

The permeation of a drug molecule across the buccal mucosa is dependent on the following.

1. Molecular size—for hydrophilic substances, as molecular weight and molecular size/radius ascends, permeability typically diminishes. Small molecular weight permeants (MW < 100 Da) are rapidly transported through buccal mucosa.

2. Lipid solubility—for non-ionizable compounds, as the lipophilicity rises, the drug permeability typically increases. To maximize the absorption rate, a drug should be available in the salivary film at its solubility limit.

3. Ionization—for ionizable drugs, maximal permeation occurs at the p^H at which ionization is least, i.e., where the drug is predominantly in the unionized form. The rate of drug absorption for the transcellular route is p^H-dependent. Such dependency results from the fact that the membrane/aqueous partition coefficient for an ionizable drug is p^H-dependent. Basement Membrane (BM). The BM has an enormous surface area compared with the epithelium owing to connective tissue papillae, which may affect the effective diffusional path length.

FORMULATIONS FOR BUCCAL MUCOADHESIVE DRUG DELIVERY [5]:

Novel dosage forms such as adhesive tablets, patches, gels, and ointments have been developed primarily for systemic delivery of therapeutic agents. These dosage forms are also capable of providing sustained drug delivery.

Buccal dosage forms can be of 1) reservoir type and 2) matrix type.

Reservoir type:

Drug formulations of the reservoir type are surrounded by a polymeric membrane, which controls the release rate. Reservoir systems present a constant release profile, provided 1) the polymeric membrane is rate limiting and 2) an excess amount of drug is present in the reservoir.

Matrix type:

Drug is uniformly dispersed in the polymer in matrix type systems, and drug release is controlled by the matrix. Drug molecules dispersed in the polymer have to dissolve in the medium and then diffuse through the polymer network. Therefore, a drug dispersion and drug-depletion zone always exists in the matrix. A thin hydrodynamic diffusion layer also exists at the interface of the drug and the matrix. A matrix system may result in a constant release profile only at early times when the drug-depletion zone is rather insignificant.

The parameters that determine the release rate of a drug from a delivery device include polymer solubility, polymer diffusivity, and thickness of the polymer diffusional path, and the drug's aqueous solubility, partition coefficient, and aqueous diffusivity. Finally, the thickness of the hydrodynamic diffusion layer, the amount of drug loaded into the matrix, and the surface area of the device all affect the drug's release rate.

Buccal adhesive tablets:

Adhesive tablets may be either monolithic or multilayered devices. Monolithic tablets can be prepared by conventional techniques of either direct compression or wet granulation. These tablets provide the possibility of holding large amounts of drug.

Using either compression or spray coating, a partial coating of every face except one that is in contact with the mucosa with a water-impermeable material such as cellophane, hydrogenated castor oil, Teflon, ethyl cellulose, etc., may cause unidirectional drug release. Multilayered tablets may be prepared by adding each formulation ingredient layer by layer into a die and by compressing it on a tablet press. These tablets can be designed to deliver drugs either systemically or locally. For multilayered tablets, incorporation of the drug into the adhesive layer, which is immediately adjacent to the mucosal surface, may aid in optimizing bioadhesion.

Buccal adhesive patches:

Adhesive patches may also be monolithic or multilayered devices of the reservoir or matrix type for either systemic or local drug delivery. Two primary types of manufacturing processes are usually used to prepare adhesive patches. These include solvent casting and direct milling (with or without a solvent). The intermediate product is a sheet from which patches are punched. A backing is then applied to control the direction of drug release and to minimize deformation and disintegration of the device during residence in the mouth. Preparation of adhesive patches by the solvent–casting method involves casting of appropriately prepared aqueous solutions of either polymer (for drug-free patches) or a drug/polymer mixture onto a backing layer sheet mounted on a stainless steel plate by means of a frame. Drying may then be performed by perfusing with a thermo stated stream of water or by air drying. The temperature is typically selected based on the excipients used in the formulation. On complete drying, the laminate may be cut into the desired shape and size using a suitable punch and a die set. Preparation of adhesive patches by direct milling is done by homogeneously mixing the drug and the bioadhesive, with or

without the aid of a solvent, using a two-roll mill. The polymer/drug mixture may then be compressed to its desired thickness, and patches of appropriate size may be cut or punched out. The polymer/drug mixture prepared with a solvent may require an additional drying step afforded by air or oven drying.

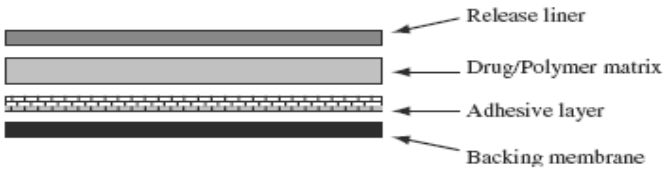


Fig.No.3: The design of mucoadhesive buccal patch.

In response to some of the drawbacks of tablets, different flexible, high-surface area, adhesive films and laminated adhesive patches have been investigated for oral mucosal drug delivery. Different polymers can be used for the development of mucosal patches, including cellulose derivatives (e.g., methylcellulose, sodium carboxymethylcellulose, hydroxyethylcellulose), natural gums (guar gum, Karaya gum, agarose), and polyacrylates, including poly(acrylic acid), poly(methacrylic acid), poly(vinylpyrrolidone), poly(ethylene glycol), and gelatin. These polymers exhibit muccoadhesive properties and form adhesive hydrogels in the presence of saliva.

The adhesive part of the system can be used as drug carrier or as an adhesive for the retention of a drug loaded non adhesive layer. In this respect a peripheral adhesive ring could be casted. The use of an impermeable backing membrane will maximize the drug concentration gradient and prolong adhesion because the system is protected from saliva.

Different types of drug release pattern from buccal patches

- Bidirectional release from adhesive patch by dissolution or diffusion;

- Unidirectional release from patch embedded in an adhesive shield;
- Bidirectional release from a laminated patch;
- Unidirectional release from a laminated patch.

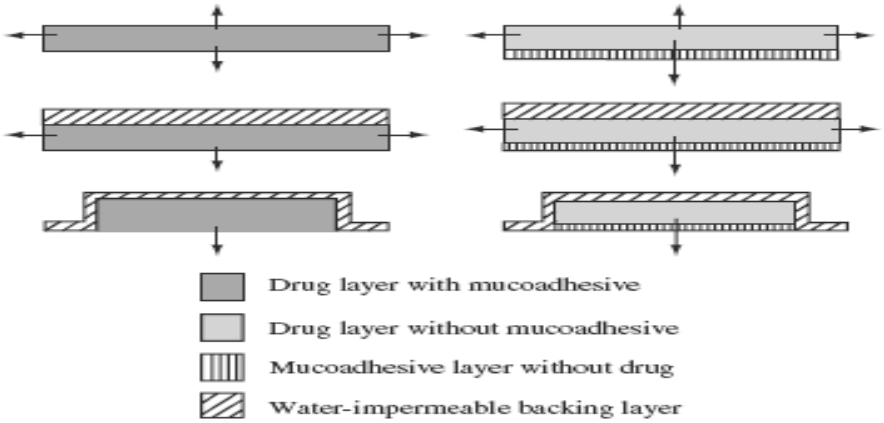


Fig.No.4: The geometric designs of buccal delivery devices.

The concept of using buccal patches as a matrix for drug delivery is not new. Buccal dosage forms offer several advantages as a drug delivery system including local delivery, rapid buccal adsorption, rapid onset, prolonged drug release, dose termination and product line extension and future products are expected soon.

1.2 DISEASE PROFILE

1.2.1 Introduction to emesis [15]:

Vomiting (known medically as emesis and informally as throwing up and by a number of other terms) is the forceful expulsion of the contents of one's stomach through the mouth and sometimes the nose. Vomiting can occur due to a wide variety of conditions; it may present as a specific response to ailments like gastritis or poisoning, or as a non-specific sequela of disorders ranging from brain tumors and elevated intracranial pressure to overexposure to ionizing radiation. The feeling that one is about to vomit is called nausea, which usually proceeds, but does not always lead to, vomiting. Antiemetic are sometimes necessary to suppress nausea and vomiting. In severe cases, where dehydration develops, intravenous fluid may be required.

Types of vomiting:

- Motion sickness
- Morning sickness(vomiting during pregnancy)
- Chemotherapy or radiation induced nausea and vomiting
- Post operative vomiting
- Vomiting of varied origin and adjuvant anti emetics

1.2.2 COMPLICATIONS:

Aspiration of vomit:

Vomiting can be dangerous if the gastric content gets into the respiratory tract. Under normal circumstances the gag reflex and coughing prevent this from occurring; however these protective reflexes are compromised in persons under the influences of

certain substances such as alcohol or anesthesia. The individual may choke and asphyxiate or suffer an aspiration pneumonia.

Dehydration and electrolyte imbalance:

Prolonged and excessive vomiting depletes the body of water (dehydration), and may alter the electrolyte status. Gastric vomiting leads to the loss of acid (protons) and chlorine directly. Combined with the resulting alkaline tide, this leads to hypochloremic metabolic alkalosis (low chloride levels together with high HCO_3 and CO_2 and increased blood p^H) and often hypokalemia (potassium depletion). The hypokalemia is an indirect result of the kidney compensating for the loss of acid. With the loss of intake of food the individual may eventually become cachectic. A less frequent occurrence results from a vomiting of intestinal contents, including bile acids and HCO_3^- , which can lead to metabolic acidosis.

Mallory-Weiss tear:

Repeated or profuse vomiting may cause erosions to the esophagus or small tears in the esophageal mucosa (Mallory-Weiss tear). This may become apparent if fresh red blood is mixed with vomit after several episodes.

Dentistry:

Recurrent vomiting, such as observed in bulimia nervosa, may lead to destruction of the tooth enamel due to the acidity of the vomit. Digestive enzymes can also have a negative effect on oral health, by degrading the tissue of the gums.

1.2.3 Pathophysiology:

Receptors on the floor of the fourth ventricle of the brain represent a chemoreceptor trigger zone, known as the area postrema, stimulation of which can lead to vomiting. The area postrema is a circumventricular organ and as such lies outside the blood-brain barrier; it can therefore be stimulated by blood-borne drugs that can stimulate vomiting or inhibit it.

There are various sources of input to the vomiting center:

- The chemoreceptor trigger zone at the base of the fourth ventricle has numerous dopamine D_2 receptors, serotonin 5-HT_3 receptors, opioid receptors, acetylcholine receptors, and receptors for substance P. Stimulation of different receptors are involved in different pathways leading to emesis, in the final common pathway substance P appears involved.
- The vestibular system, which sends information to the brain via cranial nerve VIII (vestibulocochlear nerve), plays a major role in motion sickness, and is rich in Muscarinic receptors and histamine H_1 receptors.
- The Cranial nerve X (vagus nerve) is activated when the pharynx is irritated, leading to a gag reflex.
- The Vagal and enteric nervous system inputs transmit information regarding the state of the gastrointestinal system. Irritation of the GI mucosa by chemotherapy, radiation, distention, or acute infectious gastroenteritis activates the 5-HT_3 receptors of these inputs.

- The CNS mediates vomiting that arises from psychiatric disorders and stress from higher brain centers.

The vomiting act encompasses three types of outputs initiated by the chemoreceptor trigger zone: Motor, parasympathetic nervous system (PNS), and sympathetic nervous system (SNS). They are as follows:

- Increased salivation to protect tooth enamel from stomach acids. (Excessive vomiting leads to dental erosion). This is part of the PNS output.
- The body takes a deep breath to avoid aspirating vomit.
- Retroperistalsis, starts from the middle of the small intestine and sweeps up digestive tract contents into the stomach, through the relaxed pyloric sphincter.
- Intra thoracic pressure lowers (by inspiration against a closed glottis), coupled with an increase in abdominal pressure as the abdominal muscles contract, propels stomach contents into the esophagus as the lower esophageal sphincter relaxes. The stomach itself does not contract in the process of vomiting except for at the angular notch, nor is there any retroperistalsis in the esophagus.
- Vomiting is ordinarily preceded by retching.
- Vomiting also initiates an SNS response causing both sweating and increased heart rate.

The neurotransmitters that regulate vomiting are poorly understood, but inhibitors of dopamine, histamine, and serotonin are all used to suppress vomiting, suggesting that these play a role in the initiation or maintenance of a vomiting cycle. Vasopressin and neurokinin may also participate.

1.2.4 Phases:

The vomiting act has two phases. In the retching phase, the abdominal muscles undergo a few rounds of coordinated contractions together with the diaphragm and the muscles used in respiratory inspiration. For this reason, an individual may confuse this phase with an episode of violent hiccups. In this retching phase nothing has yet been expelled. In the next phase, also termed the expulsive phase, intense pressure is formed in the stomach brought about by enormous shifts in both the diaphragm and the abdomen. These shifts are, in essence, vigorous contractions of these muscles that last for extended periods of time - much longer than a normal period of muscular contraction. The pressure is then suddenly released when the upper esophageal sphincter relaxes resulting in the expulsion of gastric contents. For people not in the habit of exercising the abdominal muscles, they may be painful for the next few days. The relief of pressure and the release of endorphins into the bloodstream after the expulsion cause the vomiter to feel better.

1.2.5 Drug treatment in emesis [11]:

Classes of antiemetic drugs:

a. **Muscarinic receptor antagonists:**

Good for prevention of motion sickness.

- scopolamine

b. **H_1 antihistamines:**

For motion sickness, most antihistamines have additional anticholinergic action. Typical side effects of H_1 antihistamines include drowsiness and loss of coordination. The newer antihistamines which do not cross the blood-brain barrier would not be useful.

- Dimenhydrinate
- Several Clizines
- Diphenhydramine
- Promethazine
- Hydroxyzine
- Meclizine

Anti dopaminergic drugs:

Most of these drugs are also used as antipsychotic agents. They have anti Muscarinic action.

- Chlorpromazine
- Droperidol (Inapsine)
- Prochlorperazine
- Metoclopramide
- Fluphenazine
- Domperidone
- Haloperidol

- Droperidol has a "black box" warning and for this reason should not be lightly used for control of emesis.

Benzodiazepines:

Good for anticipatory nausea and vomiting before cancer therapy. Also useful for vestibular disorders.

- Diazepam
- Lorazepam

Corticosteroids:

Mechanism of action not clear. May be related to the inhibition of arachidonic acid release. Dexamethasone is reportedly as effective as ondansetron for prevention of PONV

- Dexamethasone
- Methylprednisolone

Cannabinoids:

Acts on higher centers in the cortex.

Dronabinol (Rarely used until all else has failed).

5-HT_3 receptor antagonists:

This class of drugs is the most effective treatment available for prevention of severe vomiting due to cancer chemotherapy and cause little toxicity; about 85% of patients attain complete control of emesis and nausea. Usually given in combination with dexamethasone. Also widely used for PONV, but less effective. Although animal studies suggest it should not work for vestibular problems, empirically it is also often effective in this context.

- Ondansetron
- Tropisetron
- Granisetron
- Dolasetron

Miscellaneous:

- Benzquinamide
- Diphenidol -- little used because of side effects (hallucinations)
- Trimethobenzamide
- Verapamil.

2. LITERATURE REVIEW

Noha adel nafee *et al.* (2003) Mucoadhesive patches for delivery of cetylpyridinium chloride (CPC) were prepared using polyvinyl alcohol (PVA), hydroxyethylcellulose (HEC) and chitosan. Swelling and bioadhesive characteristics were determined for both plain and medicated patches. The results showed a remarkable increase in radial swelling (*S*D) after addition of the water-soluble drug (CPC) to the plain formulae. A decrease in the residence time was observed for PVA and chitosan-containing formulae. Higher drug release was obtained from PVA patches compared to HEC ones, while both are non-ionic polymers. A considerable drop in release was observed for chitosan formulae after the addition of water-soluble additives, polyvinyl pyrolidine (PVP) and gelatin. Ageing was done on PVA formulae; the results showed there was no influence on the chemical stability of CPC, as reflected from the drug content data. Physical characteristics of the studied patches showed an increase in the residence time with storage accompanied with a decrease in drug release. This may be due to changes in the crystal habit of the drug as well as to slight agglomeration of the polymer particles.

Angela Abruzzo *et al.* (2004) The aim of this work was to develop chitosan/gelatin mucoadhesive films for buccal delivery of propranolol hydrochloride, an antihypertensive agent. Buccal route ensures systemic availability, avoiding a possible drug degradation in the gastrointestinal tract and first-pass metabolism. Chitosan/gelatin complexes based films, obtained in different chitosan/gelatin weight ratio, and were prepared by a casting-solvent evaporation technique. Films were characterized by FT-IR, DSC, TGA, and in terms of thickness, morphology, drug

content uniformity and water-uptake properties. Furthermore, drug release and permeation, *in vitro* and *in vivo* mucoadhesion studies were performed[3]. Results confirmed the interaction between chitosan and gelatin. Films with a great amount of gelatin showed high water-uptake ability and provided a limited drug release and permeation, due to possible interactions between drug and gelatin. Films presented good *in vitro* and *in vivo* mucoadhesion properties and no irritative effect.

Subash Pillai *et al.* (2005) An attempt was made to formulate Buccal patches of Isoxsuprine hydrochloride, a potent and long acting vasodilator and uterine suppressant , by using Hydroxyl propyl methyl cellulose(HPMC), Polyvinyl pyrolidone K-30 (PVP K-30) and Hydroxyl ethyl cellulose (HEC). Twelve batches of buccal patches were prepared by solvent casting technique in which the best formulation was found out. The polymers HPMC, HEC, and PVP K-30 were incorporated with Isoxsuprine hydrochloride in various proportions, out of which the best formulation on the ratio (HPMC: HEC: PVPK-30-2:2:1) with the drug was determined. Prepared buccal patches were spherical, uniform in shape and white in colour. The obtained buccal films were evaluated for physicochemical characteristics, In-vitro release profile, Ex-vivo diffusion study in fresh goat cheek pouch membrane and In-vivo evaluation in rabbits. Higuchi's plot studies revealed that the predominant mechanism of drug release was diffusion.

Shiva S Krishna *et al.* (2006) Extending the residence time of a dosage form at a particular site and controlling the release of drug from the dosage form are useful especially for achieving controlled plasma level of the drug as well as improving

bioavailability. The objective of this study was to extend the GI residence time of the dosage form and control the release of rosiglitazone using mucoadhesive tablet to achieve controlled plasma level of the drug which is especially useful after 8 to 12 weeks of monotherapy using conventional dosage forms when dose is doubled and plasma level also doubles. Direct compression method using simplex lattice design, followed by optimization of the evaluation parameters was employed to get final optimized formulation. The optimized formulation showed a muccoadhesive strength >40 gm-f, and a mucoadhesion time >12 hours with release profile closer to the target release profile and followed Non-Fickian diffusion mediated release of rosiglitazone maleate.

Vishnu M. Patel *et al.* (2006) Mucoadhesive buccal patches containing propranolol hydrochloride were prepared using the solvent casting method. Chitosan was used as bioadhesive polymer and different ratios of chitosan to PVP K-30 were used. The patches were evaluated for their physical characteristics like mass variation, drug content uniformity, folding endurance, *ex vivo* mucoadhesion strength, *ex vivo* mucoadhesion time, surface pH, *in vitro* drug release, and *in vitro* buccal permeation study. Patches exhibited controlled release for a period of 7 h. The mechanism of drug release was found to be non-Fickian diffusion and followed the first-order kinetics. Incorporation of PVP K-30 generally enhanced the release rate. Swelling index was proportional to the concentration of PVP K-30. Optimized patches (F4) showed satisfactory bioadhesive strength of 9.6 ± 2.0 g, and *ex vivo* mucoadhesion time of 272 minutes. The surface pH of all patches was between 5.7 and 6.3 and hence patches should not cause irritation in the buccal cavity. Patches containing 10 mg of

drug had higher bioadhesive strength with sustained drug release as compared to patches containing 20 mg of drug. Good correlation was observed between the *in vitro* drug release and *in vitro* drug permeation with a correlation coefficient of 0.9364. Stability study of optimized patches was done in human saliva and it was found that both drug and buccal patches were stable.

Mona Semalty *et al.* (2007) For improving bioavailability in controlled release fashion and to circumvent the hepatic first pass effect of glipizide mucoadhesive buccal films of glipizide were prepared by solvent casting technique. Buccal films were prepared using hydroxy propylmethylcellulose, sodium carboxymethylcellulose, carbopol- 934P and Eudragit RL-100. Films were evaluated for their weight, thickness, surface pH, swelling index, *in vitro* residence time, folding endurance, *in vitro* release, *ex vivo* permeation studies and drug content uniformity. The films exhibited controlled release over more than 6 h. From the study it was concluded that the films containing 5 mg glipizide in 4.9 % w/v hydroxy propylmethylcellulose and 1.5 % w/v sodium carboxymethylcellulose exhibited satisfactory swelling, an optimum residence time and promising drug release thus proved to be potential candidate for the development of buccal films for therapeutic use.

S. Singh *et al.* (2008) buccal bioadhesive films, releasing topical drugs in the oral cavity at a slow and predetermined rate, provide distinct advantages over traditional dosage forms. The aim of present study was to prepare and evaluate buccal bioadhesive films of clotrimazole for oral candidiasis. The film was designed to

release the drug at a concentration above the minimum inhibitory concentration for a prolonged period of time so as to reduce the frequency of administration of the available conventional dosage forms. The different proportions of sodium carboxymethylcellulose and Carbopol 974P (CP 974P) were used for the preparation of films. Carbopol was used to incorporate the desired bioadhesiveness in the films. The films were prepared by solvent casting method and evaluated for bioadhesion, in vitro drug release and effectiveness against Candida albicans. In vitro drug release from the film was determined using a modified Franz diffusion cell while bioadhesiveness was evaluated with a modified two-arm balance using rabbit intestinal mucosa as a model tissue. Films containing 5% CP 974P of the total polymer were found to be the best with moderate swelling along with favorable bioadhesion force, residence time and in vitro drug release.

Claudia Juliano *et al.* (2008) The aim of this work was to investigate the suitability of some polymeric films as buccal systems for the delivery of the antiseptic drug Chlorhexidine diacetate, considered as a valid adjunct in the treatment of oral candidiasis. Six different film formulations, mono- or double-layered, containing 5 or 10 mg of Chlorhexidine diacetate, respectively, and alginate and/or hydroxypropylmethylcellulose and/or chitosan as excipients, were prepared by a casting-solvent evaporation technique and characterized in terms of drug content, morphology (scanning electron microscopy), drug release behavior, and swelling properties. Moreover, the in vivo concentrations of Chlorhexidine diacetate in saliva were evaluated after application of a selected formulation on the oral mucosa of healthy volunteers. The behavior of a selected formulation, chosen on the basis of its

in vitro release results, was preliminarily investigated in vivo after application in the oral cavity of healthy volunteers. The films were well tolerated and the salivary Chlorhexidine concentrations were maintained above the minimum inhibitory concentration for Candida albicans for almost 3 h. These preliminary results indicate that polymeric films can represent a valid vehicle for buccal delivery of antifungal/ antimicrobial drugs.

J. Sahni *et al.* (2008.) A buccoadhesive drug delivery system of Insulin was prepared by solvent casting technique and characterized *in vitro* by surface pH, bioadhesive strength, drug release and skin permeation studies. Sodium carboxymethylcellulose-DVP was chosen as the controlled release matrix polymer. The optimized formulation J_4 contained Sodium carboxy methyl cellulose-DVP 2% (w/v), insulin (50 IU/film), propylene glycol (0.25 ml) and Isopropyl alcohol: water (1:4) as solvent system. *In vitro* release studies were carried out at 37 ± 2° using phosphate buffer pH 6.6, in a modified dissolution apparatus fabricated for the purpose. Cumulative amount of drug released from the optimized formulation J_4 was 91.64% in 6 hours. *In vitro* permeation studies were carried out on J_4 at 37 ± 2° using Franz diffusion cell. Cumulative amount of drug permeated from J_4 was 6.63% in 6 hours. The results suggested that sodium deoxycholate 5% (w/v) was the best permeation enhancer among those evaluated. It enhanced the permeation of insulin from 6.63% to 10.38% over a period of 6 hours. The optimized patches were also satisfactory in terms of surface pH and bioadhesive strength. It can also be easily concluded that the system is a success as compared to the conventional formulations

with respect to invasiveness, requirement of trained persons for administration and most importantly, the first pass metabolism.

Mona Semalty *et al.*(2008) Mucoadhesive buccal films of glipizide were prepared by solvent casting technique using hydroxypropylmethylcellulose, sodium carboxymethylcellulose, carbopol-934P and Eudragit RL-100. Prepared films were evaluated for weight, thickness, surface pH, swelling index, *in vitro* residence time, folding endurance, *in vitro* release, permeation studies and drug content uniformity. The films exhibited controlled release over more than 6 h. From the study it was concluded that the films containing 5 mg glipizide in 4.9% w/v hydroxypropylmethylcellulose and 1.5% w/v sodium carboxymethylcellulose exhibited satisfactory swelling, an optimum residence time and promising drug release. The formulation was found to be suitable candidate for the development of buccal films for therapeutic use.

M. Nappinnai *et al.* (2008.) A mucoadhesive drug delivery system for systemic delivery of nitrendipine, a calcium channel blocker through buccal route was formulated. Mucoadhesive polymers like hydroxypropylmethylcellulose K-100, hydroxypropylcellulose, sodium carboxymethylcellulose, sodium alginate, polyvinyl alcohol, polyvinyl pyrolidine K-30 and carbopol-934P were used for film fabrication. The films were evaluated for their weight, thickness, percentage moisture absorbed and lost, surface pH, folding endurance, drug content uniformity, *In vitro* residence time, *In vitro* release and *ex vivo* permeation. Based on the evaluation of these results, it was concluded that buccal films made of hydroxypropylcellulose and sodium

carboxymethylcellulose (5±2% w/v; F-4), which showed moderate drug release (50% w/w at the end of 2 h) and satisfactory film characteristics could be selected as the best among the formulations studied.

B. K. Satishbabu *et al.* (2008.) This paper describes the preparation of new bilayered device comprising a drug containing mucoadhesive layer and a drug free backing layer. Bilaminated films were produced by a casting/ solvent evaporation technique. The mucoadhesive layer was composed of mixture of drug and sodium alginate with or without carbopol 934 P, and backing layer was made of ethyl cellulose. The double layer structure design was expected to provide drug delivery in a unidirectional fashion to the mucosa and avoid loss of drug due to wash out with saliva. The fabricated films were subjected to *in vitro* drug release, *in vitro* permeation through porcine buccal mucosa. The bilayered films were also evaluated for mucoadhesive strength, mucoadhesive time, folding endurance, hydration studies and tensile strength.

Soad A. Yehia *et al.* (2009) Fluconazole mucoadhesive buccal films were prepared using film forming polymers namely; hydroxypropylmethylcellulose (HPMC), hydroxyethyl cellulose (HEC), chitosan, Eudragit and sodium alginate (SALG) either alone or in combination with bioadhesive polymers. The bioadhesive polymers studied were sodium carboxymethyl cellulose (SCMC), Carbopol 974P, and polycarbophil (AA-A). The prepared films were characterized by means of film thickness, surface pH, swelling capacity, *in vitro* adhesion, *in vivo* residence time, *in vitro* drug release and *in vivo* drug release to determine the amount of drug release

from selected film formulae using microbiological assay and HPLC. Optimum release behavior, convenient bioadhesion, acceptable elasticity were exhibited by film containing 2% HPMC and 1% SCMC (fresh or stored for 6 months). Determination of the amount of drug released in saliva after application of the selected fluconazole films confirmed the ability of the film to deliver the drug over a period of approximately 300 minutes and to reduce side effects and possibility of drug interaction encountered during systemic therapy of fluconazole, which would be beneficial in the case of oral candidiasis.

Amit Khairnar *et al.* (2009) Mucoadhesive buccal patch of Aceclofenac were prepared using polymer like Gelatin, Poly Sodium CMC and Poly Vinyl Alcohol. Eight formulations were prepared with varying the concentration of Poly Sodium CMC and evaluated for various parameters like weight variation, patch thickness, volume entrapment efficiency %, and measurement of % elongation at break, folding endurance, i*n vitro* mucoadhesive time, *in vitro* release and stability study. The formulations showed a sustained release. The F5 formulation containing Aceclofenac 6%, Gelatin 4.5%, Poly Sodium CMC 5.5%, Propylene Glycol 5%, Poly vinyl Alcohol 2.5% and Distilled Water up to 100%, showed a release of 88.4% after 8 hours. The Aceclofenac stability studies were performed at 40 ± 2 0C / 75 ± 5% RH. Among the eight formulation, F5 formulation showed maximum desired properties release.

M. Alagusundaram *et al.* (2009) Bioadhesive formulations have a wide scope of application for both systemic and local effects of drugs. The mucosa is relatively permeable, well supplied with both vascular and lymphatic drainage. The oral

transmucosal drug delivery bypasses liver and avoids presystemic elimination in the gastro intestinal tract and liver. The present investigation highlights the formulation and evaluation of mucoadhesive buccal films of ranitidine. The mucoadhesive buccal films of ranitidine were prepared by solvent casting technique using polymers like hydroxy propyl methyl cellulose-15 cps and poly vinyl pyrrolidone. The formulated films were evaluated for their physiochemical parameters like surface pH, percentage moisture absorption, percentage moisture loss, swelling percentage, water vapour transmission rate, thickness, weight of the films, folding endurance and drug content. *In vitro* release studies were performed with pH 6.8 phosphate buffer solution. Good results were obtained both in physico chemical characteristics and *in vitro* studies. The films exhibited controlled release more than 10 h. The *in vitro* release data were fit to different equations and kinetic models to explain release profiles. The correlation coefficient value (r) indicates the kinetic of drug release was zero order. The formulation was found to be right and suitable candidate for the formulation of ranitidine buccal film for therapeutic use.

Y. Vamshi Vishnu *et al.* (2007) A buccal patch for systemic administration of carvedilol in the oral cavity has been developed using two different mucoadhesive polymers. The formulations were tested for *in vitro* drug permeation studies, buccal absorption test, *in vitro* release studies, moisture absorption studies and *in vitro* bioadhesion studies. The physicochemical interactions between carvedilol and polymers were investigated by Fourier transform infrared (FTIR) Spectroscopy. According to FTIR the drug did not show any evidence of an interaction with the polymers used and was present in an unchanged state. XRD studies reveal that the

drug is in crystalline state in the polymer matrix. The results indicate that suitable bioadhesive buccal patches with desired permeability could be prepared. Bioavailability studies in healthy pigs reveal that carvedilol has got good buccal absorption. The bioavailability of carvedilol from buccal patches has increased 2.29 folds when compared to that of oral solution. The formulation AC5 (HPMC E 15) shows 84.85 + 0.089% release and 38.69 + 6.61% permeated through porcine buccal membrane in 4 hr. The basic pharmacokinetic parameters like the Cmax, Tmax and AUCtotal were calculated and showed statistically significant difference ($P<0.05$) when given by buccal route compared to that of oral solution.

Rajesh Singh Patel *et al.* (2009) Mucoadhesive patch releasing the drug in the oral cavity at predetermined rate may present distinct advantages over traditional dosage forms such as tablets, gels and solutions. The present study was concerned with the preparation and evaluation of mucoadhesive buccal patches for the controlled systemic delivery of Salbutamol sulphate to avoid first pass hepatic metabolism. The developed patches were evaluated for the physicochemical, mechanical and drug release characteristics. The patches showed desired mechanical and physicochemical properties to withstand environment of oral cavity. The *in-vitro* release study showed that patches could deliver drug to the oral mucosa for a period of 7 h. the patches exhibited adequate stability when tested under accelerated conditions.

Vishnu M. Patel *et al.* (2009) Mucoadhesive buccal patches containing propranolol hydrochloride were prepared using solvent casting method was develop and evaluate for in-vitro performance using hydrophobic polymer eudragit L-100. In

preparation of patches hydrophilic polymers like carbopol-934 and PVP K-30 were incorporated to modify bioadhesive properties, and drug release rate. Patches were evaluated for surface pH, folding endurance, swelling index, ex-vivo mucoadhesive strength, in-vitro drug release and in-vitro buccal permeation. The prepared patches were smooth, elegant in appearance, uniform in thickness, weight, and drug content and showed no visible cracks and showing good folding endurance. Results indicates that the high amount of carbopol 934 and low amount of PVP K30 favor the ex-vivo mucoadhesive strength of the patches but low amount of carbopol 934 and high amount of PVP K30 favor the dissolution rate (t50, t80) and swelling index of the patches. It can be concluded from present study that mucoadhesive patches of eudragit could be a useful carrier in buccal drug delivery systems.

Chandra Sekhar Kolli *et al.* (2009) The aim of this investigation was to develop and evaluate mucoadhesive buccal patches of prochlorperazine (PCPZ). Permeation of PCPZ was calculated *in vitro* using porcine buccal membrane. Buccal formulations were developed by solvent-casting technique using hydroxy propylmethyl cellulose (HPMC) as mucoadhesive polymer. The patches were evaluated for *in vitro* release, moisture absorption and mechanical properties. The optimized formulation, based on *in vitro* release and moisture absorption studies, was subjected for bioadhesion studies using porcine buccal membrane. *In vitro* flux of PCPZ was calculated to be 2.14 ± 0.01 μg. h–1.cm–2 and buccal absorption was also demonstrated *in vivo* in human volunteers. *In vitro* drug release and moisture absorbed was governed by HPMC content. Increasing concentration of HPMC delayed the drug release. All formulations followed Zero order release kinetics whereas the release pattern was non-Fickian. The mechanical properties, tensile

strength (10.28 ± 2.27 kg mm–2 for formulation P3) and elongation at break reveal that the formulations were found to be strong but not brittle. The peak detachment force and work of adhesion for formulation P3 were 0.68 ± 0.15 N and 0.14 ± 0.08 mJ, respectively. The results indicate that suitable bioadhesive buccal patches of PCPZ with desired permeability and suitable mechanical properties could be prepared.

R.S. Hirlekar *et al.* (2009) Carvedilol is an antihypertensive drug used in the treatment of congestive heart failure, cardiac arrhythmias and angina pectoris. It exhibits poor bioavailability of 25-30% which is attributed to its poor solubility and high first pass metabolism. The present work was aimed at overcoming these two limitations. Drug-Methyl-β-cyclodextrin complex was prepared by kneading method and characterized by Fourier Transformation Infrared spectroscopy, Differential Scanning Calorimetry and powder X-Ray Diffractometry studies. Dissolution rate of complex was compared with plain drug and physical mixture. The complex was incorporated into buccal tablet. The buccal tablets were evaluated for drug release, mucoadhesive strength and ex-vivo permeability. Characterization of binary system revealed the formation of inclusion complex of drug with Methyl-β-cyclodextrin. The complex showed complete release as compared to 32.8% and 42.7% from plain drug and physical mixture respectively in 60min. Tablets containing complex showed complete release at the end of 180min compared to 40.23% from tablets containing plain drug. The buccal tablets containing complex had good mucoadhesive strength. The amount of drug permeated from these tablets across the porcine buccal mucosa at the end of 5h was 6.2mg as compared to 2.51mg from tablets containing plain drug.

Thus it can be concluded that buccal tablet containing complexed CAR would have improvement in bioavailability.

Subhash V. Deshmane *et al.* (2009) The buccal region of the oral cavity is an attractive target for administration of the drug of choice. Sustained release formulations have been developed and are gaining in popularity and medical acceptance. To increase bioavailability and prevent first pass metabolism of drug, verapamil hydrochloride was embedded in sustained released buccal patch over period of 6 hour. The objective of present work was to characterize the effect of chitosan with PVP K-30 on water soluble drug by preparing mucoadhesive buccal patch. Each formulated batch was subjected to various evaluation parameters. The swelling percentage was found to be function of solubility of drug and PVP K-30. The mucoadhesive strength, vapour transmission and in-vitro released of water soluble drug through water insoluble chitosan base matrix were found satisfactorily. The physical appearance of buccal patch was examined by scanning electron microscopy. The released kinetic model best to fit for the optimized batch was Hixson Crowell, indicating that the drug release from systems in which there is a change in the surface area and the diameter of particles present in dosage form.

Surya N. Ratha Adhikari *et al.*(2010) Buccal patches for the delivery of atenolol using sodium alginate with various hydrophilic polymers like Carbopol 934 P, sodium carboxymethyl cellulose, and hydroxypropylmethylcellulose in various proportions and combinations were fabricated by solvent casting technique. Various physic mechanical parameters like weight variation, thickness, folding endurance,

drug content, moisture content, moisture absorption, and various ex vivo mucoadhesion parameters like mucoadhesive strength, force of adhesion, and bond strength were evaluated. An in vitro drug release study was designed, and it was carried out using commercial semi permeable membrane. All these fabricated patches were sustained for 24 h and obeyed first-order release kinetics. Ex vivo drug permeation study was also performed using porcine buccal mucosa and various drug permeation parameters like flux and lag time were determined.

A Semalty *et al.* (2010.) Enalapril maleate is used in the treatment of hypertension and angina pectoris. It shows low bioavailability due to high hepatic first pass metabolism. Hence the present work was undertaken to formulate mucoadhesive buccal films of Enalapril maleate with an objective to improve therapeutic efficacy, patient compliance and the bioavailability. In the present study ten formulations of mucoadhesive drug delivery system of Enalapril maleate were prepared as buccal films, by solvent casting technique. Sodium carboxymethylcellulose, hydroxyl propyl methyl cellulose, hydroxyethylcellulose and polyvinyl pyrolidine K-90 were used as mucoadhesive polymers. Prepared films were evaluated for their weight, thickness, surface pH, swelling index, drug content uniformity, *in vitro* residence time, folding endurance *in vitro* release and permeation studies. Films exhibited controlled release over more than 10 h in permeation studies. It was concluded that the films containing 20 mg of Enalapril maleate in sodium carboxymethylcellulose 2% w/v and hydroxyethylcellulose 2% w/v (formulation F5), showed good swelling, a convenient residence time and promising controlled drug release, thus can be selected for the development of buccal film for effective therapeutic uses.

Rahamatullah Shaikh *et al.* (2010) Mucoadhesion is commonly defined as the adhesion between two materials, at least one of which is a mucosal surface. Over the past few decades, mucosal drug delivery has received a great deal of attention. Mucoadhesive dosage forms may be designed to enable prolonged retention at the site of application, providing a controlled rate of drug release for improved therapeutic outcome. Application of dosage forms to mucosal surfaces may be of benefit to drug molecules not amenable to the oral route, such as those that undergo acid degradation or extensive first-pass metabolism. The mucoadhesive ability of a dosage form is dependent upon a variety of factors, including the nature of the mucosal tissue and the physicochemical properties of the polymeric formulation. This review article aims to provide an overview of the various aspects of mucoadhesion, mucoadhesive materials, factors affecting mucoadhesion, evaluating methods, and finally various mucoadhesive drug delivery systems (buccal, nasal, ocular, gastro, vaginal, and rectal).

Rana M. Obaidat *et al.* (2010.) The specific aim of this work was to prepare mucoadhesive patches containing tetracycline hydrochloride and carvacrol in an attempt to develop a novel oral drug delivery system for the treatment of mouth infections. The bilayered patches were prepared using ethyl cellulose as a backing layer and carbopol 934 as a matrix mucoadhesive layer. Patches were prepared with different loading amounts of tetracycline hydrochloride and carvacrol. The antimicrobial activity was assessed for the prepared patches using the disc-diffusion method against the yeast *Candida albicans* and five bacterial strains, including *Pseudomonas aeruginosa*, *Escherichia coli*, *Bacillus cereus*, *Staphylococcus aureus*,

and *Bacillus bronchispti*. In this work, we highlighted the possibility of occurrence of a synergistic action between carvacrol and tetracycline. The best formulation was selected based on microbiological tests, drug release, *ex-vivo* mucoadhesive performance, and swelling index. Physical characteristics of the selected formulations were determined. These included pH, patch thickness, weight uniformity, content uniformity, folding endurance, and patch stability.

Sathish Dharani *et al.* (2010) The goal of the present investigation was to design and evaluate mucoadhesive buccal patches of Ondansetron Hydrochloride (OND) which is used for nausea and vomiting associated with cancer chemotherapy and radiotherapy. Permeation of OND was calculated *ex vivo* using porcine buccal membrane. Buccal films were developed by solvent-casting technique using Hydroxy Propyl Methyl Cellulose(HPMC E15) as mucoadhesive polymer. The patches were evaluated for weight variation, thickness variation, surface pH, moisture absorption, *in vitro* residence time, mechanical properties, *in vitro* release, *ex vivo* permeation studies and drug content uniformity. The formulation F3 was found to give the better results and obeys first order kinetics.

Rohit Chaudhary *et al.* (2010) The goal of present investigation was to design and evaluate mucoadhesive bilayered buccal devices comprising a drug containing mucoadhesive layer and a drug free backing membrane. Bilaminatd patches composed of mixture of drug (Methotrexate) and sodium alginate alone or in combination with sodium carboxy methylcellulose ,Polyvinylpyrrolidine and carbopol 934 and backing membrane (Ethyl cellulose).The patches were fabricated by solvent

casting technique and were evaluated for In-Vitro and Ex-Vivo drug release. The patches were evaluated for film weight uniformity, thickness, swelling index, surface pH, mucoadhesive strength and mucoadhesive time and folding endurance. A combination of sodium alginate with carbopol-934 and glycerol as plasticizer gives promising results. The optimized patch exhibit an in vitro release of 82% through cellophane membrane and 70.78 % through buccal mucosa with satisfactory mucoadhesive strength and mucoadhesive time.

Marina Koland *et al.* (2010) Buccal delivery is considered to be an important alternative to the peroral route for the systemic administration of drugs. Losartan potassium is an angiotensin II receptor antagonist with an oral bioavailability of only 33% due to extensive first pass metabolism. Mucoadhesive buccal films of losartan potassium were prepared using hydroxypropyl methyl cellulose (HPMC) and retardant polymers ethyl cellulose (EC) or eudragit RS 100. Thermal analysis by DSC of formulations show no interaction between drug and polymers. Ex vivo permeation studies of losartan potassium solution through porcine buccal mucosa showed 90.2 % absorption at the end of 2 hours. The films were subjected to physical investigations such as uniformity of thickness, weight, drug content, folding endurance, tensile strength, elongation at break, surface pH and mucoadhesive strength. Films were flexible and those formulated from EC were smooth whereas those prepared from Eudragit were slightly rough in texture. The mucoadhesive force, swelling index, tensile strength and percentage elongation at break was higher for those formulations containing higher percentage of HPMC. In vitro drug release studies reveal that all films exhibited sustained release in the range of 90.10 to 97.40 % for a period of 6

hours. The data was subjected to kinetic analysis which indicated non Fickian diffusion for all formulations except E2. Ex vivo permeation studies through porcine buccal mucosa indicate that films containing higher percentage of the mucoadhesive polymer HPMC showed slower permeation of the drug for 6-7 hours.

Vijendra Suryawanshi *et al.* (2010) Buccoadhesive tablets have long been employed to improve the bioavailability of drugs undergoing significant first pass hepatic metabolism. Dimenhydrinate is an anti-emetic drug. It was under goes extensive first pass metabolism resulting in an oral bioavailability of 46 % and it shows variable absorption from GIT. Buccal route offers several advantages such as rapid absorption, high plasma concentration level and ease of administration and termination of therapy. The present investigation concerns the development of Buccoadhesive tablets of Dimenhydrinate which were designed to prolong the buccal residence time after oral administration. Buccal tablets of Dimenhydrinate were formulated using four mucoadhesive polymers namely, Carbopol 934 P, HPMC K4M, HPMC K15M and Sodium carboxymethylcellulose carried out studies for weight variation, thickness, hardness, content uniformity, swelling index, Bioadhesive force and in vitro drug release. Formulation of F5 were formulated by using polymers Carbopol 934 P and Sodium carboxymethylcellulose provided controlled release of Dimenhydrinate over period of 8 hrs. The cumulative % of drug release of formulation F5 were 96.67. In-vitro releases of F1 to F9 were found to be diffusion controlled and followed zero order kinetics. The stability studies showed that there was no significant change in adhesive strength, in-vitro release when stored at room temperature, 40oC, 2-8 ^{o}C for a period of 30 days. Formulation of F5 which were

formulated by using polymers Carbopol 934 P and Sodium carboxymethylcellulose were established to be the optimum formulation with optimum bioadhesive force, swelling index & desired in-vitro drug release. Further investigations are needed to confirm the in-vivo efficiency, long term stability studies are needed to stabilize the controlled released (F5) formulations.

D. Sandeep kumar *et al.* (2010) The goal of the present investigation was to design and evaluate mucoadhesive bi-layered buccal devices comprising a drug containing mucoadhesive layer and a drug free backing membrane. Bilaminated films composed of mixture of drug (lornoxicam) and chitosan, with hydroxyl-propyl methylcellulose (15 cps) and backing layer (ethyl cellulose). Films were fabricated by solvent casting technique and were evaluated for thickness, drug content uniformity, bio-adhesion strength, percent, swelling index, folding endurance and in vitro drug release. A combination of chitosan and hydroxylpropyl methylcellulose (1:1) using propylene glycol (50% by weight of polymer) as plasticizer gave promising results. The optimized film exhibited an In vitro drug release of approximately 90% in 5 hrs along with satisfactory bio-adhesive strength. Promising film was tested for drug excipient interaction (FTIR). FTIR spectra indicated that there are no drug-excipient interactions.

3.1 DRUG PROFILE

DIMENHYDRINATE

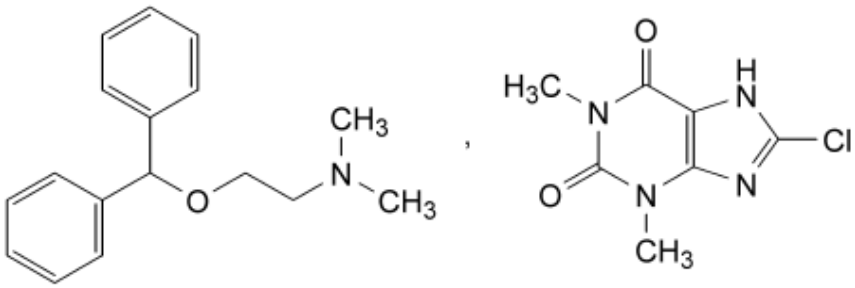
Generic name:

Dimenhydrinatum, Diphenhydrinate, Dramamine, Gravol and Vertirosan.

Description:

Dimenhydrinate is an over-the-counter drug used to prevent motion sickness. It is closely related to diphenhydramine HCl, or Benadryl. It is primarily a H1-antagonist, but also possesses an antimuscarinic effect.

Structure:



Molecular formula:

$C_{24}H_{28}ClN_5O_3$

Chemical name:

8-chloro-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-7-ide;[2-(diphenylmethoxy) ethyl]dimethylazanium

Melting point:

102 °C to 106 °C.

Molecular weight:

469.964

Solubility:

Water solubility 3000 mg/L, Insoluble in Acids and Alkalines.

Therapeutic class:

Used for treating vertigo, motion sickness, and nausea associated with pregnancy.

Storage:

Store in an airtight container, protected from light.

Pharmacokinetic parameters

Absorption:

Well absorbed after oral administration.

Distribution:

Probably widely distributed into body tissues; crosses the placenta; small amounts in breast milk but no information about crossing blood brain barrier.

Metabolism:

Hepatic (cytochrome P-450 system)

Elimination:

Renal route.

Duration of action:

4-6 hours

Mechanism of action/effect:

The mechanism by which some antihistamines exert their antiemetic, anti–motion sickness, and antivertigo effects is not precisely known but may be related to their central anticholinergic actions. They diminish vestibular stimulation and depress labyrinthine function. An action on the medullary chemoreceptive trigger zone may also be involved in the antiemetic effect. Dimenhydrinate is a competitive antagonist at the histamine H_1 receptor, which is widely distributed in the human brain. Dimenhydrinate's anti-emetic effect is probably due to H_1 antagonism in the vestibular system in the brain.

Precautions to consider:

Symptoms of overdose include delirium, hallucinations, and excitement. Patients may be violent and confused.

Side/adverse effects:

Drowsiness, confusion, restlessness, headache, dizziness, blurring of vision

Indications:

Treatment of nausea and vomiting caused by drug or motion sickness.

3.2 EXCIPIENT PROFILE

3.2.1 HYDROXY PROPYL METHYL CELLULOSE E15

Non-proprietary names:

Hypromellose, Hydroxyl propyl methyl cellulose2208, 2906.

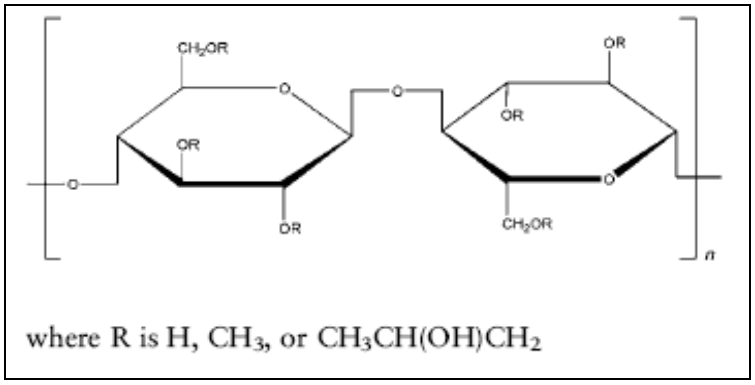
Synonyms:

Methyl hydroxyl propyl cellulose, propylene glycol ether of methyl cellulose, methyl cellulose propylene glycol ether.

Description:

An odorless, tasteless, white or creamy white colored fibrous or granular powder.

Structural formula:



Chemical name:

Cellulose, 2-hydroxypropylmethyl ether, cellulose hydroxypropylmethyl ether

Molecular weight:

Approximately 86,000

Functional category:

Coating agent, film former, tablet binder, stabilizing agent, suspending agent, viscosity increasing agent, and emulsion stabilizer.

Density:

Bulk Density -0.341 g/cm^3

Tapped Density -0.557 g/cm^3

True Density -1.326 g/cm^3

Solubility:

Soluble in cold water forming viscous colloidal solution, insoluble in chloroform, alcohol and ether, but soluble in methanol and methylene chloride.

Viscosity:

15 mPas

Stability and storage conditions:

Very stable in dry conditions. Solutions are stable at P^H 3.0-11.0.

Store in a tight container, in a cool place.

Incompatibilities:

Extreme P^H conditions, oxidizing materials.

Safety:

Human and animal feeding studies have shown HPMC to be safe.

3.2.2 HYDROXY ETHYL CELLULOSE

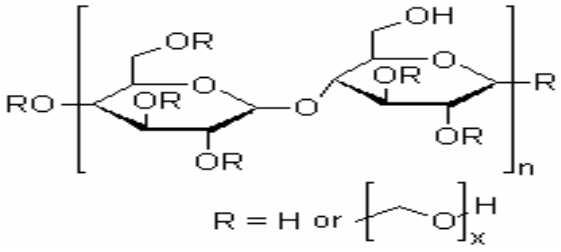
Synonyms:

Hydroxyethyl ether, Hydroxyethylcellulose, 2-hydroxyethyl cellulose

Description:

Hydroxy ethyl cellulose is a gelling and thickening agent derived from cellulose. It is widely used in cosmetics, cleaning solutions, and other household products. Hydroxyethyl cellulose and methyl cellulose are frequently used with hydrophobic drugs in capsule formulations, to improve the drugs' dissolution in the gastrointestinal fluids. This process is known as "Hydrophilization"

Structural formula:



Chemical name:

2-hydroxyethyl ether

Melting point:

Softens at 135–140^{0}C, decomposes at about 205^{0}C.

Functional category:

HEC is mainly used as adhesive protective gelatin, thicker agent and stabilizing agent as well as additives to make emulsion, frozen gelatin, lotion, eye clear agent, suppository and tablets. HEC is also used for hydrophilic colloid, framework, material, ready-made framework controlled release agent, and stabilizing agent in foodstuff.

Apparent density:

0.35–0.61 g/cm^3

Solubility:

It can dissolve in other cool or hot water. Normally, it does not dissolve in organic solvents. Viscosity change is small when pH value is within 2 to 12 but decrease when p^H value is low than the range.

Viscosity:

5 - 100,000mPa.s

Stability and storage conditions:

Keep dry in ventilated places and keep away from sunshine during transportation

Incompatibilities:

Hydroxy ethyl cellulose is insoluble in most organic solvents. It is incompatible with zein and partially compatible with the following water-soluble compounds: casein, gelatin, methylcellulose, polyvinyl alcohol and starch.

Safety:

Hydroxy ethyl cellulose is primarily used in ophthalmic and topical pharmaceutical formulations. It is generally regarded as an essentially nontoxic and nonirritant material.

3.2.3 POLY VINYL PYRROLIDINE

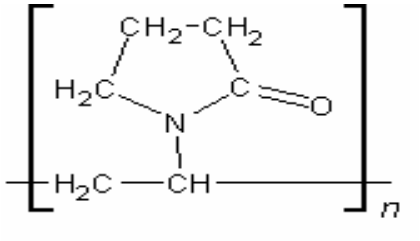
Synonyms:

PVP, Povidone, Polyvidone

Description:

PVP is soluble in water and other polar solvents. When dry it is a light flaky powder, which readily absorbs up to 40% of its weight in atmospheric water. In solution, it has excellent wetting properties and readily forms films. This makes it good as a coating or an additive to coatings.

Structural formula:



Molecular formula:

$(C_6H_9NO)_n$

Chemical name:

Polyvinylpyrrolidine

Melting point:

150-180^{0}c

Functional category:

It is used as a binder in many pharmaceutical tablets

Apparent density:

1.2 g/cm³

Solubility:

Soluble in hot and cold water.

Stability and storage conditions:

Stable, Incompatible with strong oxidizing agents, Light sensitive, Hygroscopic.

Store at room temperature.

Safety:

It is generally considered safe. However, there have been documented cases of allergic reactions to PVP/Povidone, particularly regarding subcutaneous (applied under the skin) use and situations where the PVP has come in contact with autologous serum (internal blood fluids) and mucous membranes.

Polyvinylpyrrolidine may cause interstitial fibrosis in the lungs. Lesions regress when patient is no longer being exposed to the compound.

3.2.4 POLY VINYL ALCOHOL

Non proprietary names:

Poly (vinylis acetas), Poly vinyl alcohol.

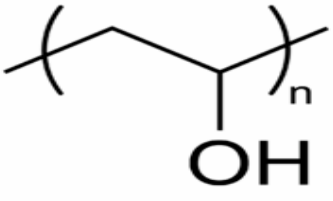
Synonyms:

Poly (Ethenol), Ethenol, Homopolymer, PVA, Polyviol, Vinol, Alvyl, Alkotex, Covol, Gelvatol, Lemol, Mowiol.

Description:

Polyvinyl alcohol occurs as an odorless, white to cream-colored granular powder.

Structural formula:



Chemical name:

Poly Vinyl Alcohol

Molecular formula:

CH_2CHOH

Molecular weight:

$(44.05)_n$ g/mole

Functional category:

Coating agent, lubricant, stabilizing agent, viscosity-increasing agent.

Apparent density:

1.19-1.31 g/cm³

Solubility:

Soluble in cold water, hot water. Insoluble in diethyl ether, acetone, petroleum solvents, aromatic hydrocarbons, esters.

Practically insoluble in animal and vegetable oils and chlorinated hydrocarbons.

Melting Point:

Softens at about 200°C (392°F) with decomposition. Decomposition at 228^0C.

Incompatibilities:

Reactive with oxidizing agents, metals, acids, alkalis.

Safety:

Polyvinyl alcohol is generally considered a nontoxic material. It is nonirritant to the skin and eyes at concentrations up to 10%, concentrations up to 7% are used in cosmetics.

Storage:

Keep container tightly closed. Keep container in a cool, well-ventilated area.

3.2.5 PROPYLENE GLYCOL

Non-proprietary names:

Propylenglycolum, Propylene glycol

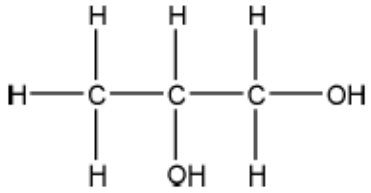
Synonyms:

2-hydroxypropanol; methyl ethylene glycol; methyl glycol; propane-1,2-diol.

Description:

Propylene glycol is a clear, colorless, viscous, practically odorless liquid with a sweet, slightly acrid taste resembling that of glycerin.

Structural formula:



Chemical name:

1, 2-Propanediol

Molecular weight:

76.09

Functional category:

Antimicrobial preservative, Disinfectant, Humectants, Plasticizer, Solvent, Stabilizer for vitamins, Water-miscible co solvent.

Apparent density:

1.038 g/cm^3 at 208^{0}C

Solubility:

Miscible with acetone, chloroform, ethanol (95%), glycerin, and water; soluble at 1 in 6 parts of ether; not miscible with light mineral oil or fixed oils, but will dissolve some essential oils.

Viscosity:

58.1 mPas (58.1 cP) at 208^0C

Stability and storage conditions:

At cool temperatures, propylene glycol is stable in a well-closed container, but at high temperatures, in the open, it tends to oxidize, giving rise to products such as propionaldehyde, lactic acid, pyruvic acid, and acetic acid. Propylene glycol is chemically stable when mixed with ethanol (95%), glycerin, or water; aqueous solutions may be sterilized by autoclaving. Propylene glycol is hygroscopic and should be stored in a well-closed container, protected from light, in a cool, dry place.

Incompatibilities:

Propylene glycol is incompatible with oxidizing reagents such as potassium permanganate.

Safety:

Propylene glycol is used in a wide variety of pharmaceutical formulations and is generally regarded as a relatively nontoxic material.

4.1 RESEARCH OBJECTIVE

Transmucosal route of drug delivery have more advantages than oral administration for systemic drug delivery. Oral mucosal drug delivery is the route designed to deliver a therapeutically effective amount of drug across the mucosal surface of a patient and will have the following advantages.

- Better bioavailability
- Bypassing first-pass metabolism.
- Avoidance of presystemic elimination of drug in GIT.
- Reduction of side effects.
- To produce controlled release of drug.
- Localization of drug to oral cavity.
- An ideal route of administration of drug for pregnant ladies and post operative vomiting.

Dimenhydrinate is a member of drug belonging to the class of H_1 anti histamine used in treatment of post operative vomiting. Dimenhydrinate undergoes first pass metabolism in the liver and as a consequence the availability of Dimenhydrinate in general circulation is low and variable.

Physicochemical properties of Dimenhydrinate like small dose lipophilicity, stability at buccal P^H, tasteless odorless and more absorption through buccal mucosa makes it an ideal candidate for administration by buccal route.

Hence in the present work an attempt is being made to formulate a buccal muccoadhesive dosage form for Dimenhydrinate in the form of buccal patches by

using four different polymers Hydroxy Propyl Methyl Cellulose (HPMC), Hydroxy Ethyl Cellulose (HEC), Poly Vinyl Alcohol (PVA), Poly Vinyl Pyrolidine (PVP) to overcome the Hepatic metabolism and low bioavailability.

4.2 PLAN OF WORK

1. Preformulation studies
    a) Solubility determination
    b) Melting point determination.
    c) Compatibility studies between Dimenhydrinate and polymers used.
2. Preparation of standard curve for Dimenhydrinate.
3. Formulation of buccal patches of Dimenhydrinate using different polymers in different concentrations.
4. Evaluation of muccoadhesive buccal patches for following parameters
    a) Physical parameters
        i. Thickness
        ii. Folding endurance
        iii. Measurement of surface P^H
        iv. Water uptake study
    b) Performance parameters
        i. Drug content uniformity
        ii. Measurement of bioadhesive strength
        iii. Mechanical strength
        iv. Scanning electron microscopy (SEM)
        v. In-vitro release study
        vi. Invitro residence time
        vii. Ex-vivo drug release study
        viii. Stability study
        ix. Kinetic study

The results are presented in tables and graphically by various equations governing release kinetics.

5. METHODOLOGY

The following materials & instruments were used for the preparation of Dimenhydrinate buccal patches.

Table No. 1: LIST OF CHEMICALS USED

S.no	Name	Grade	supplier
1	Dimenhydrinate	Pharma	Aurabindo pharmaceuticals.
2	HPMC E15	USP/EP	Alkem laboratories
3	Hydroxy ethyl cellulose	Laboratory	SD Fine Chemicals Ltd. Mumbai.
4	Poly vinyl alcohol	Laboratory	SD Fine Chemicals Ltd. Mumbai.
5	Poly vinyl pyrolidine	Laboratory	SD Fine Chemicals Ltd. Mumbai.
6	Propylene glycol	Laboratory	SD Fine Chemicals Ltd. Mumbai.
7	Potassium dihydrogen phosphate	Laboratory	SD Fine Chemicals Ltd. Mumbai.
8	Disodium hydrogen phosphate	Laboratory	SD Fine Chemicals Ltd. Mumbai.
9	Distilled water	Laboratory	-----

LIST OF INSTRUMENTS

Table No.2: LIST OF INSTRUMENTS USED

S.no.	Name	supplier
1.	Magnetic Stirrer	NEBO, India.
2.	Electronic Digital Balance	SCHIMADZU, Japan.
3.	Teflon coated Magnetic Beads	Modern Scientific Works, Coimbatore.
4.	Digital P^H Meter.	SYSTRONIC, Chennai
5.	Franz diffusion cell	Glass works, New Delhi.
6.	Double Beam UV/VIS Spectrophotomèter.	SYSTRONIC, Chennai
7.	Hot Air Oven	KEMI, India.
8.	Vaccum Dessicator	Polylab, India
9.	FT-IR	Perkin Elmer, US.
10.	Incubator	KEMI, India
11.	Screwguage	SOMET INOX, INDIA
12.	Whatmann filter paper	Minisart, Germany

1. PREFORMULATION STUDIES:

Preformulation testing first step in development of dosage forms of a drug. It is defined as an investigation of physical chemical properties of drug substance alone and when combined with excipients. The overall concept of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms.

The goals of the Preformulation studies are:

- To establish the necessary physicochemical properties of a new drug substance.
- To determine its kinetic release profile.
- To establish its compatibility with different excipients.

Hence, Preformulation studies on the obtained sample of drug include physical tests and compatibility studies.

A. Identification tests:

- **IR spectroscopy:** The IR spectrum of the obtained sample of drug was compared with the IR spectra of the pure drug.
- **Solubility analysis:** Solubility analysis was done to select a suitable solvent system to dissolve the drug and to test its solubility in the dissolution medium, witch was to be used.
- **Melting point determination:** Melting point of drug sample was determined by capillary tube method.

B. Compatibility studies of Dimenhydrinate and polymers:

FT-IR spectrum of drug and physical mixture of drug with polymers were obtained. The samples were mixed with KBr and the spectrum was obtained by scanning over the wave number range of 4000-400cm^{-1}. IR helps to confirm the identity of the drug and to detect the interaction of the drug with the excipients.

C. Calibration curve.

A. Scanning of drug:

Accurately weighed 100mg of Dimenhydrinate and dissolved in 10ml of methanol and make up the volume to 100ml with distilled water. Take one ml from the above solution and make up the volume to 100ml with distilled water having concentration of 10mcg/ml

The absorption maxima of the above standard solution was scanned between 200-400nm in UV spectrophotometer against blank. The absorption maxima were found to be **276nm.**

B. **Preparation of calibration curve of Dimenhydrinate**

From the above standard solution aliquots of 1,2,3,4,5,6,7,8,9,10ml was withdrawn and the volume make up to 10ml with distilled water to get the concentration of 1-10mcg/ml respectively. Absorbances of these solutions were measured against blank at 276nm.

PREPARATION OF BUCCAL PATCHES:

Patches containing Dimenhydrinate and HPMC E15, HEC, PVP, PVA different proportions was prepared by the solvent casting method. The drug was dissolved in 5ml of methanol and the polymers were dissolved in separate container with 20ml of distilled water under continuous stirring for 4 hours. After stirring, mix the drug and polymer solution. Propylene glycol was added into the solution as a plasticizer under constant stirring. The viscous solution was left over night to ensure a clear, bubble free solution. The solution was poured into a glass petridish and allowed to dry at 40^0c temperature till a flexible patch was formed. Dried patch was removed carefully, checked any imperfections or air bubbles and cut into pieces of $1mm^2$ area. The patches were packed in aluminum foil and stored in desiccators to maintain the integrity and elasticity of the patches. Table no.3 shows the composition of different buccal patches.

Table no. 3: composition of buccal patches of Dimenhydrinate.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Dimenhydrinate	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg
HPMC E15	750 mg	----	250 mg	375 mg	500 mg	750 mg	----	250 mg	375 mg	500 mg
HEC	----	750 mg	500 mg	375 mg	250 mg	----	750 mg	500 mg	375 mg	250 mg
PVP	125 mg	125 mg	125 mg	125 mg	125 mg	----	----	----	----	----
PVA	----	----	----	----	----	125 mg	125 mg	125 mg	125 mg	125 mg
ETHANOL	5ml	5ml	5ml	5ml	5ml	5ml	5ml	5ml	5ml	5ml
Propylene glycol	0.7 ml	0.7 ml	0.7 ml	0.7 ml	0.7 ml	0.7 ml	0.7 ml	0.7 ml	0.7 ml	0.7 ml
Distilled water	25ml	25ml	25ml	25ml	25ml	25ml	25ml	25ml	25ml	25ml

EVALUATION OF MUCCOADHESIVE BUCCAL PATCHES OF DIMENHYDRINATE

- Physical parameters
    - v. Thickness
    - vi. Folding endurance
    - vii. Measurement of surface P^H
    - viii. Water uptake study
- Performance parameters
    - x. Drug content uniformity
    - xi. Measurement of bioadhesive strength
    - xii. Mechanical strength
    - xiii. Scanning electron microscopy (SEM)
    - xiv. In-vitro release study
    - xv. Invitro residence time
    - xvi. Ex-vivo drug release study
    - xvii. Stability study
    - xviii. Kinetic study

A. PHYSICAL PARAMETERS:

a) Thickness of patch:

Thickness of patch was measured at 5 different randomly selected spots using screw gauge. The mean and standard were calculated.

b) Folding endurance:

Folding endurance of the buccal patches was determined by taking 20mm diameter of patch was repeatedly folding at the same place till it broke. The no of times of patch could be folded at the same place without breaking gave the value of the folding endurance. The test was done three times and calculates the mean and standard.

c) Mechanical strength:

Mechanical properties of patches were evaluated by using the microprocessor based advanced force gauze equipped with a motorized test stand equipped with cell. Patch with diameter 60×10mm and without any visual defects were cut and positioned between two clamps separated by a distance 3cm. clamps were designed to secure the patch without crushing it during test, the lower clamp was held stationary and the strips were pulled apart by the upper clamp moving at a rate 2mm/sec until the patch broke. The force and elongation of the film at the point when the patch broke was recorded. The tensile strength and elongation at break values were calculated using the formula.

$$\text{Tensile strength } (kg.mm^{-2}) = \frac{\text{Force at break (kg)}}{\text{Initial cross sectional area of the sample } (mm^2)}$$

$$\text{Elongation at break } (\%.mm^{-2}) = \frac{\text{Increase in length (mm)}}{\text{Original length}} \times \frac{100}{\text{Cross sectional area } (mm^2)}$$

WATER UPTAKE STUDY

The moisture uptake studies give an indication about the relative moisture absorption capacities of polymers and an idea whether the formulations maintain their integrity after absorption of moisture. This test was carried out by dissolving 5% w/v agar in hot water. It was transferred into petriplates and it was allowed to solidify. Six drug free patches from each formulation were selected and weighed. They were placed in vacuum oven overnight prior to the study to remove moisture if any and laminated on one side with water impermeable backing membrane. They were then incubated at 37^0 C for one hour, removed and reweighed. The percentage moisture absorption was calculated by using the formula.

$$\% \text{ Moisture absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

This test was performed in triplicate.

Surface p^H

For determination of surface pH three films of each formulation were allowed to swell for 2 h on the surface of an agar plate. The surface P^H was measured by using a P^H paper placed on the surface of the swollen patch. A mean of three readings was recorded.

B. PERFORMANCE PARAMETERS:

a) Drug content uniformity:

Drug content uniformity was calculated by taking three film units of each formulation were taken in separate 100 ml volumetric flasks, 100 ml of P^H 6.8 phosphate buffer was added and continuously stirred for 24 hrs. The solutions were filtered, diluted suitably and analyzed at 276nm in a UV spectrophotometer (Sysronic). The average of drug contents of three films was taken as final reading.

b) Measurement of bioadhesive strength:

The force required to detach the bioadhesive films from the mucosal surface was applied as a measure of the bioadhesive performance. Bioadhesive strength of the patches was examined by the slightly modified procedure using the porcine gastric mucosa as the model membrane. The instrument is broadly composed of a modified two arm physical balance in which the right pan had been replaced by a formulation holding glass plate and counter balanced by a water collecting pan suspended to the left arm. The pan received a siphon tube from a 10 L bottle, which was kept at a high place in such a way that water head in the bottle, always remains above the water collecting pan. The siphon tube bears a flow regulating device. Nylon thread was used to suspend both the glass plate and the pan. An acrylate tissue mounting stage was attached to the center of a glass beaker. Glass beaker was filled with phosphate buffer (P^H 6.8) to simulate in-vivo saliva conditions. A magnetic stirrer provided with temperature control was used to maintain the temperature of phosphate buffer (P^H 6.8) in glass dish at 37±0.5 °C. A piece of porcine gastric mucosa, 3 cm long, was tightly secured on the upper surface of the acrylate tissue mounting stage with thread. Films

were fixed on the centre of the formulation holding glass plate with an adhesive. The exposed film surface was moistened with phosphate buffer (P^H 6.8) and left for some time for initial hydration and swelling. Then glass plate (with the film) was kept on the mucosal tissue secured on the tissue mounting stage in such a way that films completely remained in contact with mucosa. The whole assembly was kept undisturbed for few minutes (preload time) to establish the adhesion between the film and mucosal tissue. The glass plate (weight 50 g) itself acted as a preload. After the preload time, water collecting pan was suspended to the left arm and water was added in it, by the siphon tube, at a constant rate of 200 drops per minute until detachment of the film from mucosal surface took place. A support was kept under the water collecting pan to hold it at the time of detachment. Weight of water collected in the pan at the time of detachment was measured. The experiment was performed in triplicate.

Measurement of *in vitro* Residence Time

The *in vitro* residence time was determined by using modified USP disintegration apparatus. The disintegration medium was 800 ml of isotonic Phosphate buffer solution (P^H 6.8) taken and maintained at temperature 37 ± 2^0C. The segments of porcine buccal mucosa, each of 3 cm length, were glued to the surface of a glass slab, which was then vertically attached to the apparatus. Three muccoadhesive films of each formulation were hydrated on one surface using isotonic Phosphate buffer solution (P^H 6.8) and the hydrated surface was brought into contact with the mucosal membrane. The glass slab was vertically fixed to the apparatus and allowed to move up and down. The film was completely immersed in the buffer

solution at the lowest point and was out at the highest point. The time required for complete erosion or detachment of the film from the mucosal surface was recorded.

Scanning electron microscopy:

SEM has been used to determine the particle size distribution, surface texture and to examine the morphology of the fractured or sectioned surface. The same generally used for generating three dimensional surface relief images derived from secondary electrons. The examination of surface of polymeric drug delivery can provide important information about the porosity and microtecture of device.

***Invitro* release study by dissolution [4]:**

The US pharmacopoeia XXIII rotating paddle method was used to study and calculate the drug release from the buccal patches, 500ml of phosphate buffer used as the dissolution medium at 37 ± 0.5^0c and a rotation speed 50RPM was used. Patches of $1cm^2$ area were cutted and sandwiching the patch in dialysis membrane. A piece of glass slide was placed as support to prevent the assembly from floating. The dialysis membrane tubing with patch inside was secured from both ends using closure clips, then it was placed in the bottom of the vessel containing phosphate buffer having p^H 6.8. Samples 5ml were withdrawn at a specific time interval and replaced with fresh buffer medium. The samples were filtered using whatmann filter paper and analyzed by using UV spectrophotometer at 276nm. The experiments were performed triplicate and average values were calculated and reported.

Ex-vivo release study [4]:

Ex-vivo release studies performed by using the buccal tissue from porcine was collected from slaughter house. The tissue was excised to remove fat and muscle using scalpel and then placed in phosphate buffer p^H 7.4. The buccal epithelium was

carefully mounted between two compartments of Franz diffusion cell with internal volume 60ml. Phosphate buffer p^H 7.4 was placed in receptor compartment and the donor compartment containing 4ml of phosphate buffer in which the drug was dissolved. The entire setup was placed on magnetic stirrer and temperature maintained at 37^0c. The patch was moisten and attached to the buccal mucosa. The epithelium with buccal patch was placed between the two compartments. Samples of 3ml was collected from the receptor side at predetermined time interval and replaced with equal amount of fresh buffer solution. The samples were analyzed by using UV spectrophotometer at 276nm.

Stability studies:

Stability of a drug has been defined as the ability of a particulate formulation, in a specific container, to remain with in its physical, chemical, therapeutic and toxicological specifications.

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, and enables recommended storage conditions.

ICH specifies the length of study and storage conditions:

Long term testing – $25^0c\pm2^0c$/ 60%±5% RH for 12 months

Accelerated testing – $40^0c\pm2^0c$/ 75%±5% RH for 6 months

Procedure:

In the present study, stability studies were carried out for a specific time period up to 90days, for selected formulations at $40^0c \pm 2^0c$/ 75%±5% RH in humidity control oven for 30days.

The selected formulation F3 was analyzed for the physical parameters like general surface pH, water absorption studies and performance parameters like drug content uniformity, Invitro dissolution studies, and Ex-vivo permeation study.

Kinetic study:

The matrix systems were reported to follow the zero order release rate and the diffusion mechanism for the release of the drug. To analyze the mechanism for the release and release rate kinetics of the dosage form, the data obtained was fitted into, Zero order, First order, Higuchi matrix and peppa's model. In this by comparing the r-values obtained, the best fit model was selected.

1. Zero order kinetics:

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly, assuming that the area does not change and no equilibrium conditions are obtained can be represented by the following equation

$$Q_t = Q_o + K_o t$$

Where Q_t is the amount of drug dissolved in time t, Q_o is the initial amount of drug in the solution and K_o is the zero order release constant.

2. First order kinetics:

To study the first order release kinetics the release rate data were fitted to the following equation.

$$\text{Log } Q_t = \log Q_o + k_1 t/2.303.$$

Where Q_t is the amount of the drug released in time t, Q_o is the initial amount of the drug in the solution and K_1 is the first order release constant.

3. Higuchi model:

Higuchi developed several theoretical models to study the release of water soluble and low soluble drugs incorporated in semisolids and or solid matrices. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media. And the equation is

$$Q_t = K_H . t^{1/2}$$

Where Q_t is the amount of drug released in time t, K_H is the Higuchi dissolution constant.

4. Korsmeyer and Peppa's model:

To study this model the release rate data are fitted to the following equation.

$$M_t/M_\infty = K.t^n$$

Where M_t/M_∞ is the fraction of drug release, K is the release constant, t is the release time and n is the Diffusional exponent for the drug release that is dependent on the shape of the matrix dosage form.

6. RESULTS

1. Preformulation studies:

A. Identification of pure drug:

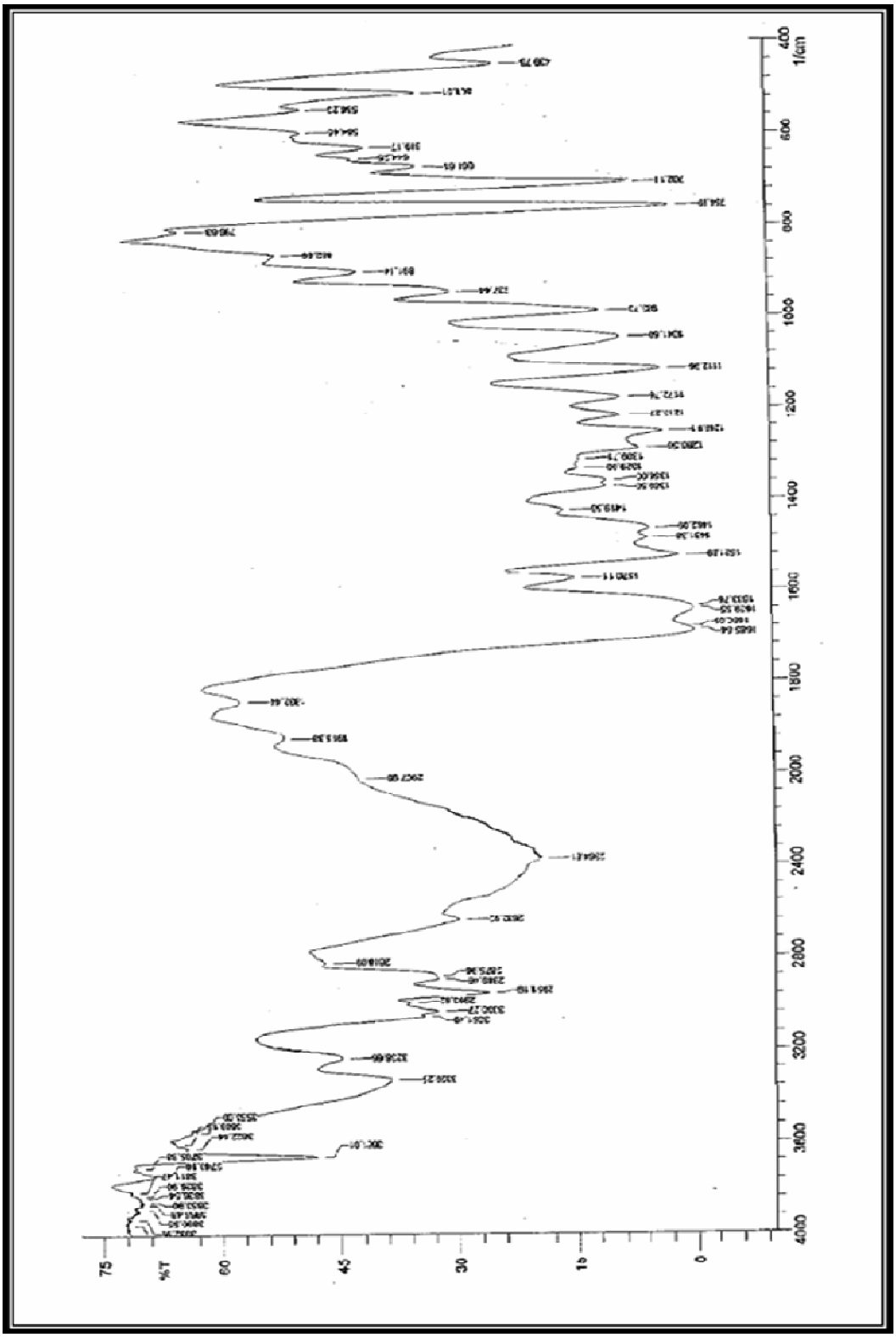
IR Spectroscopy:

The IR spectrum of pure drug of Dimenhydrinate shows the following functional groups at their frequencies. The IR spectra of Dimenhydrinate shown in spectrum no.1

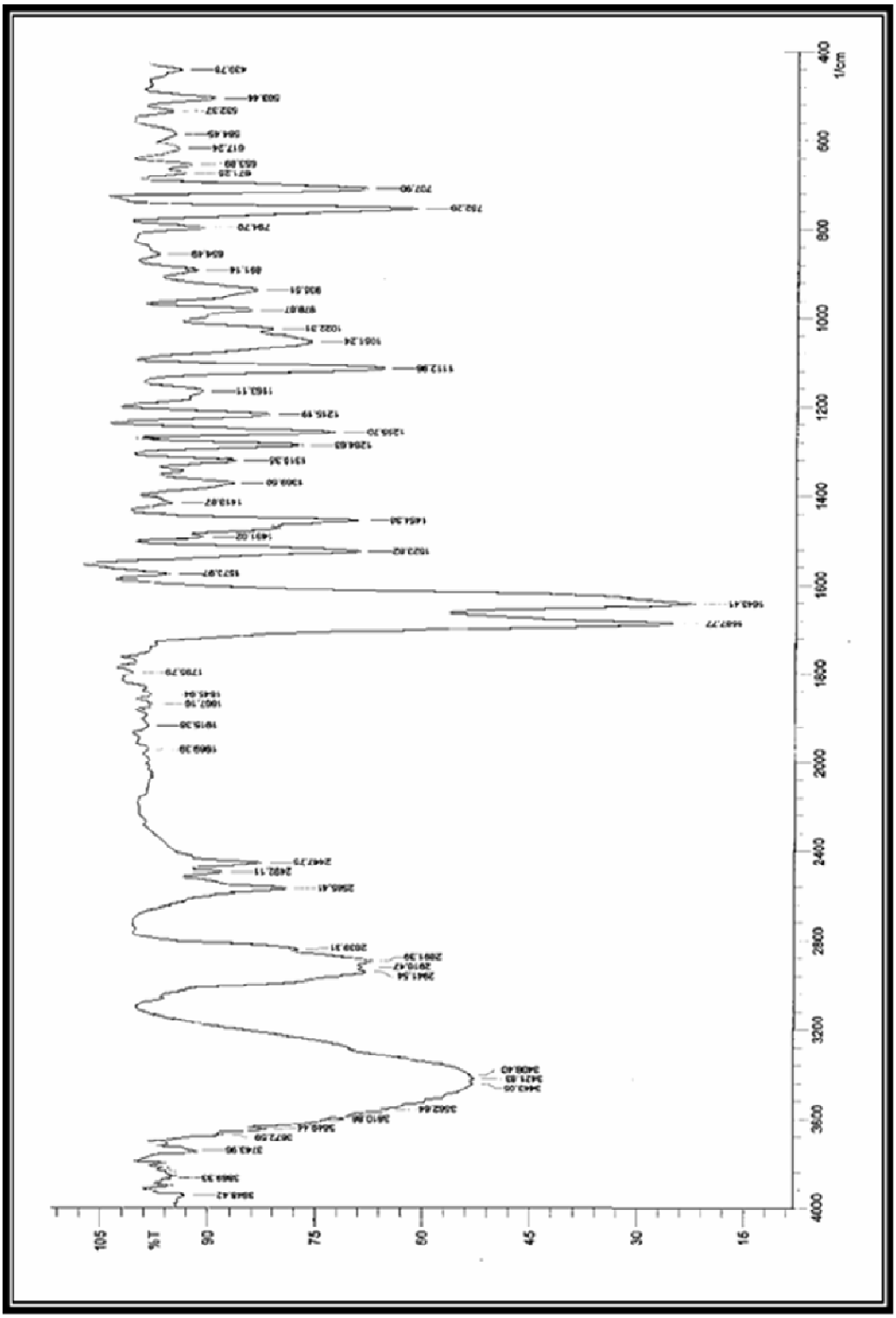
Table No. 4 Interpretation of IR spectra

S.no	Functional group	IR range	Assessment of peak(cm^{-1})
1	C-H Stretching in CH_3 group	1020-1220	1041.60
2	C-H Stretching in aromatic ring	3100-3000	3030.27
3	N-H Stretching in Hetero aromatic ring	3500-3220	3329.25
4	C-Cl Stretching of mono chlorinated aromatic compound	750-700	702.11
5	C-H Stretching in Methoxy group	2815-2850	2818.09
6	C-H Bending vibration in CH_2 group of R-CH2-N=	1475-1445	1462.09

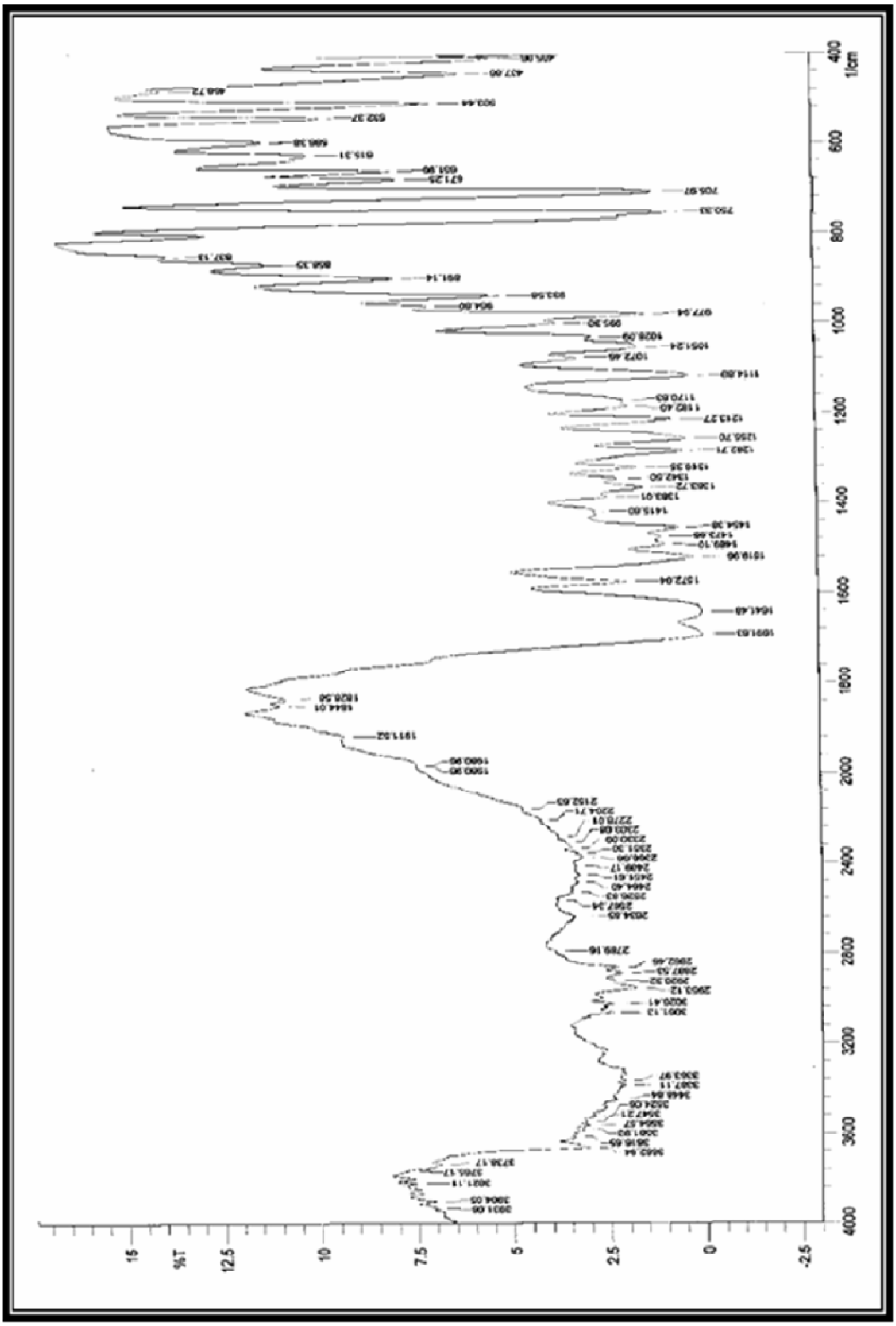
Spectrum No.1: FT-IR Spectra of drug (Dimenhydrinate)



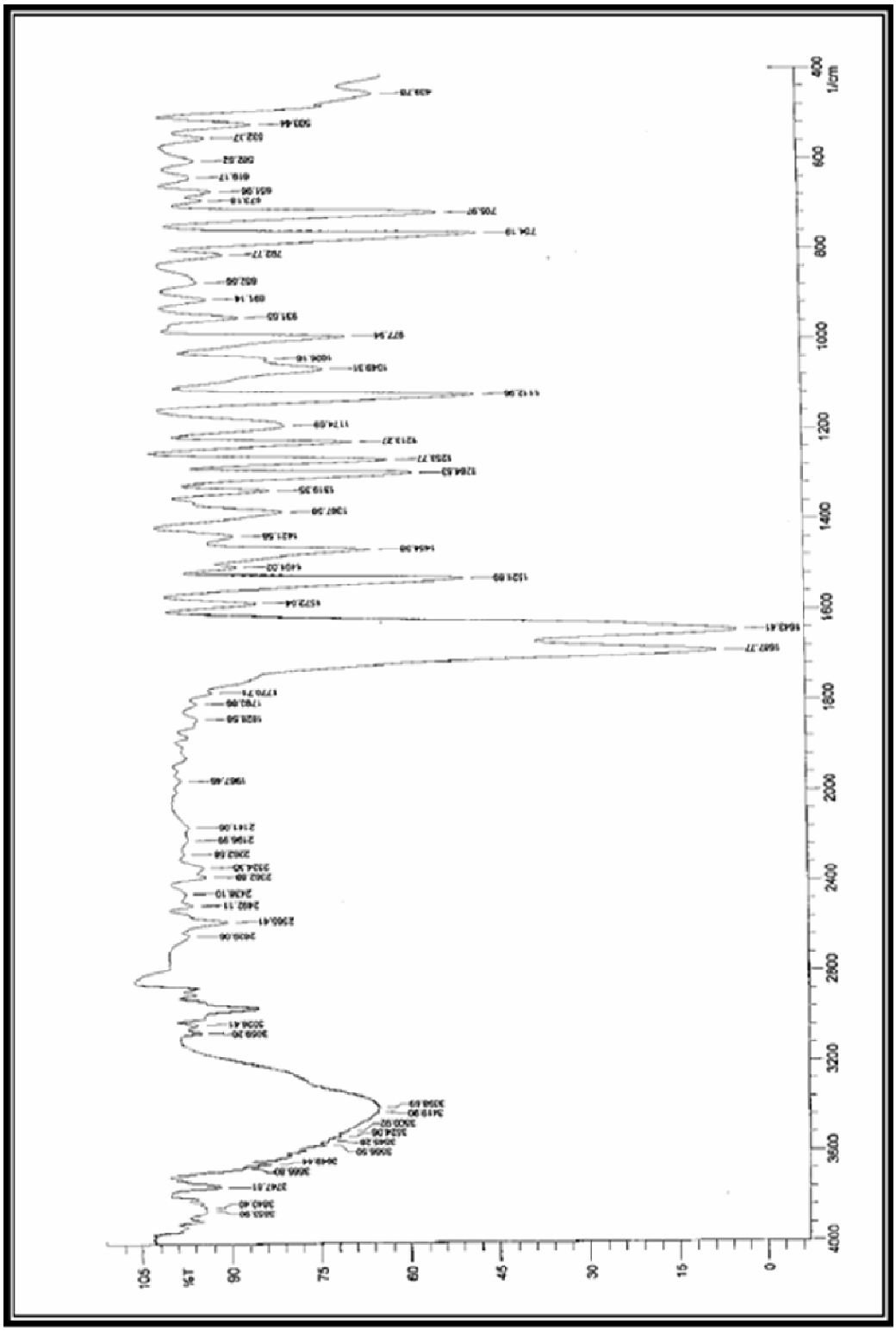
Spectrum No.2: FT-IR Spectra of drug (Dimenhydrinate) + HPMC E15



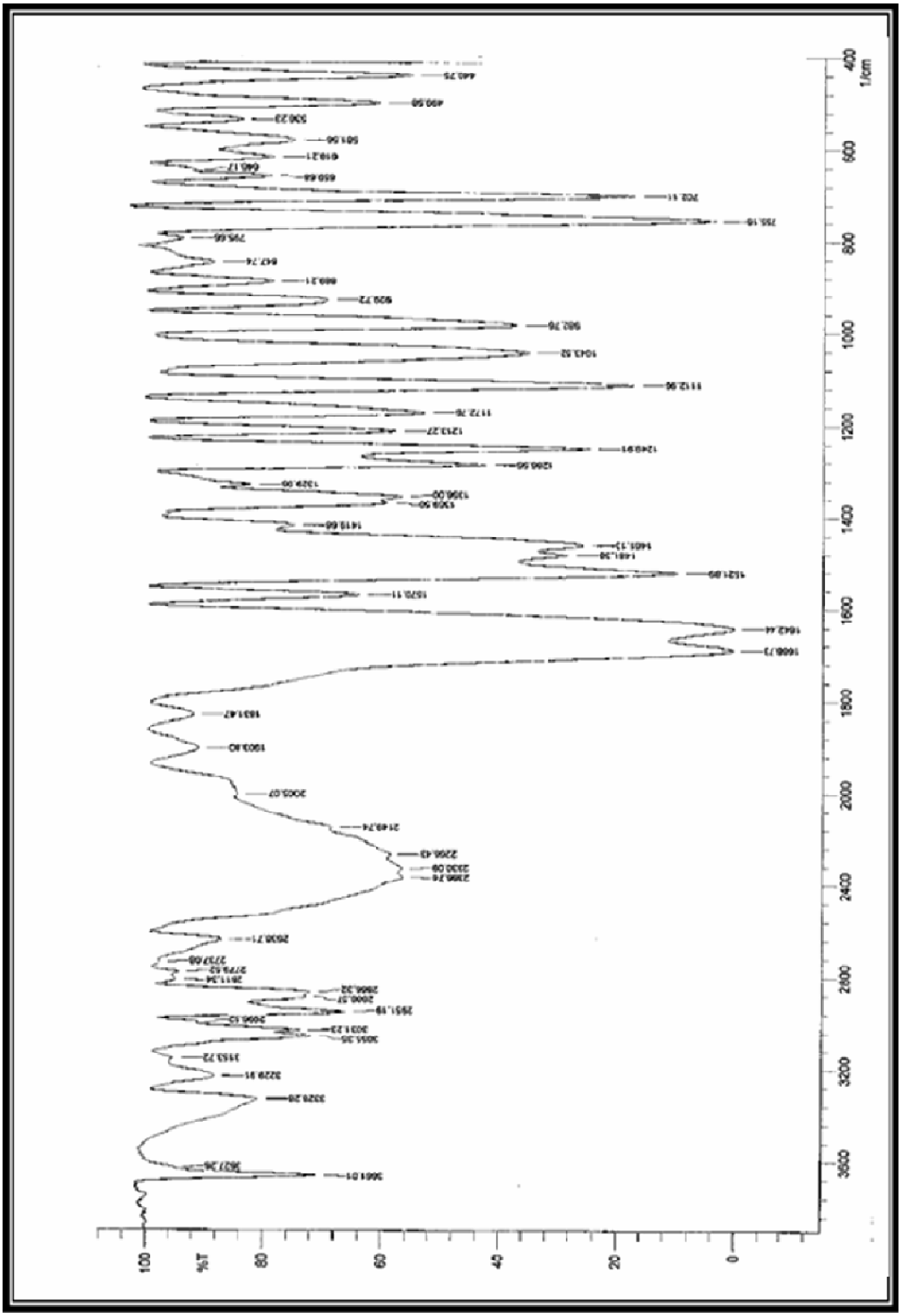
Spectrum No.3: FT-IR Spectra of drug (Dimenhydrinate) + HEC



Spectrum No.4: FT-IR Spectra of drug (Dimenhydrinate) + PVP



Spectrum No.5: FT-IR Spectra of drug (Dimenhydrinate) + PVA



Solubility study:

The approximate solubility's of substances are indicated by the descriptive terms in the accompanying table no 7.

Table no .5 Descriptive term for solubility

Descriptive term	Parts of solvent required for 1 part of solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10000
Practically in soluble or insoluble	Greater than or equal to 10000

1. Dimenhydrinate – soluble in methanol, ethanol and water, insoluble in acids.

Melting point determination:

The melting point of the drug sample was found to be, which is with in the reported value of 104^0c.it complies with standards thus indicating the purity of drug sample.

Drug –excipients compatibility studies:

From IR spectra of pure drug and the combination of pure drug with polymers, shows that all the characteristic peaks of Dimenhydrinate were present in the combination spectrum thus indicating compatibility of the drug and polymer.

IR spectra of pure drug and in combination with the polymers are shown in spectrum.

Calibration curve of Dimenhydrinate in distilled water:

Table no.7 shows the absorbance of Dimenhydrinate standard solution containing 1-10mcg/ml of drug in distilled water. Graph no shows a representative calibration curve with slope and regression coefficient, 0.018 and 0.999 respectively. The curve was found to be linear in the range of 1-10mcg/ml at absorbance maxima 276nm.

Spectrum No.6: Absorption maxima scanning of Dimenhydrinate.

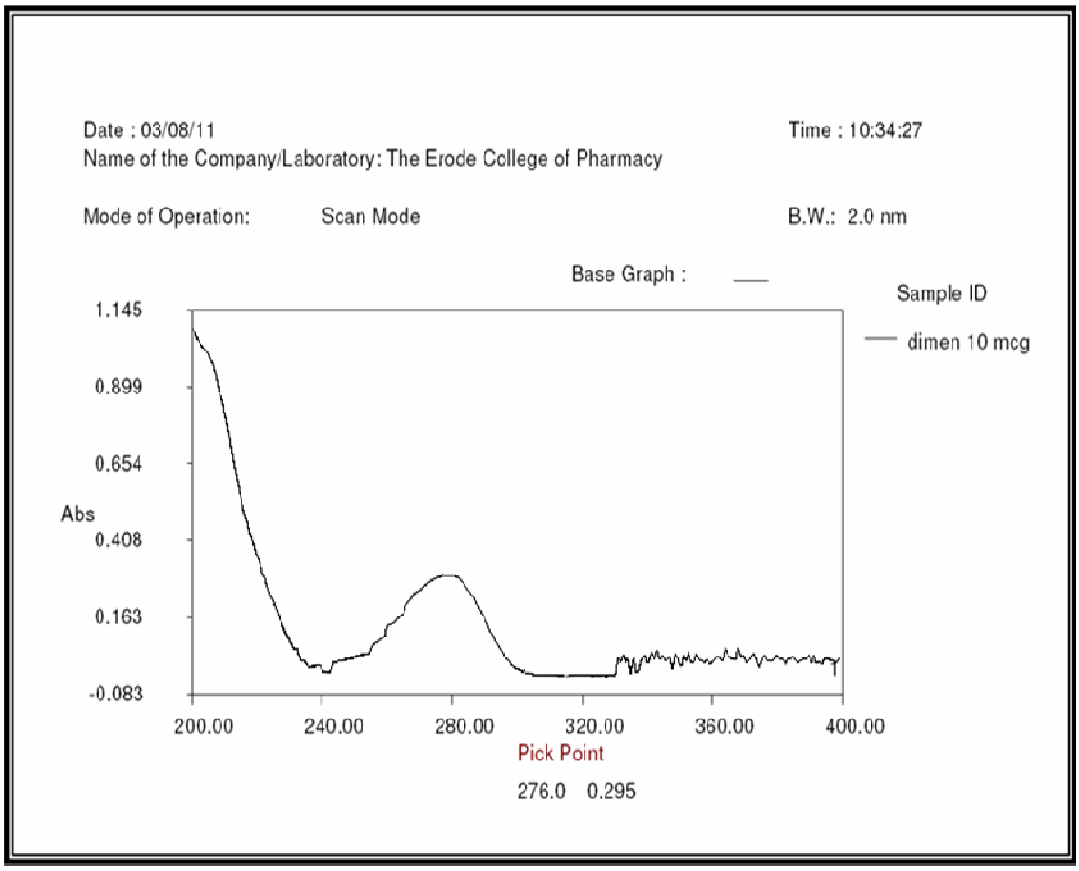
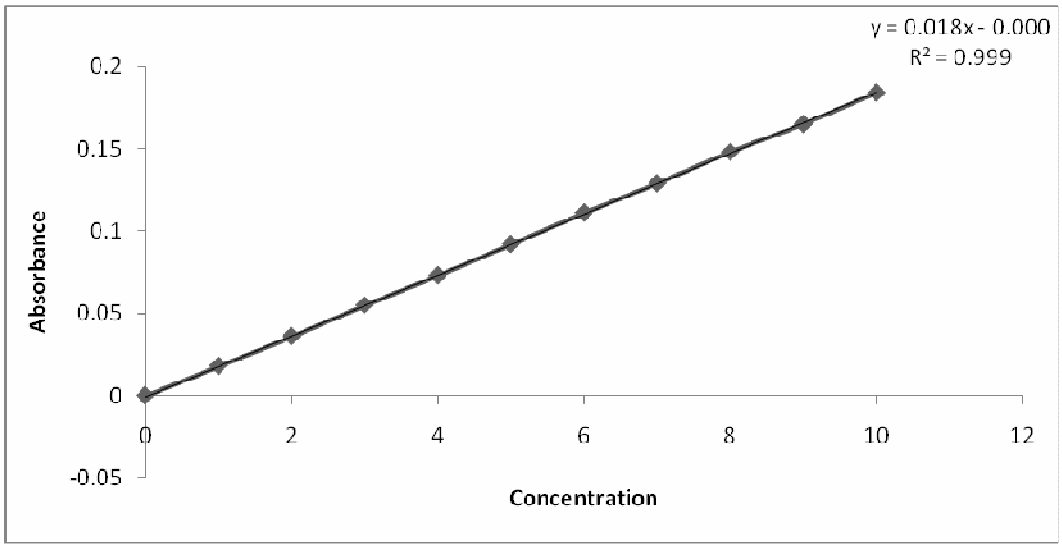


TABLE NO.7: STANDARD CURVE OF DIMENHYRINATE USING DISTILLED WATER.

S.NO	Concentration(mcg/ml)	Absorbance
1	0	0
2	1	0.018
3	2	0.036
4	3	0.055
5	4	0.073
6	5	0.092
7	6	0.111
8	7	0.129
9	8	0.148
10	9	0.165
11	10	0.184

Graph No.5: STANDARD CALIBRATION CURVE FOR DIMENHYRINATE IN DISTILLED WATER.



EVALUATION PARAMETERS:

Physical properties:

Thickness of patch:

The thickness of the prepared buccal patches of each formulation was determined with in the range of 0.23- 0.26mm. Is given in table no.8.

Folding endurance:

The folding endurance of each formulation was determined with in the range of 302 to 318. Is given in table no.8.

Mechanical strength:

Three patches of each formulation were evaluated and mean values are recorded in table no.8. The values were found to be in the range of 5.28 to 12.94kg/mm^2. The values revealed that the patches were having good mechanical strength.

Water uptake study:

Water uptake of all buccal patches containing Dimenhydrinate is given in table no.8. These values represent the mean of three replicate determinations. The values were found to be with in the range of 1.93 to 2.93. The percentage water absorption of the respective patches was determined at Third hour.

Table.no.8: Evaluation of Physical parameters of different mucoadhesive buccal patches of Dimenhydrinate.

Formulation code	Physical parameters			
	Thickness (mm) ±S.D (n=3)	Folding endurance ±S.D (n=3)	Mechanical strength ±S.D (n=3) (kg/mm^2)	Water uptake ±S.D (n=3)
F1	0.23± 0.005	305± 4.04	5.28± 0.076	2.15± 0.64
F2	0.22± 0.014	305± 4.72	6.04± 0.056	2.02± 0.52
F3	0.24± 0.002	313± 2.51	12.94± 0.098	2.93± 0.102
F4	0.26± 0.0023	318± 2.51	12.64± 0.124	2.53± 0.23
F5	0.25± 0.001	302± 1.00	10.86± 0.132	1.95± 0.051
F6	0.23± 0.003	312± 2.51	6.84± 0.079	1.93± 0.153
F7	0.24± 0.023	318± 2.52	7.23± 0.32	2.07± 0.354
F8	0.26± 0.01	310± 5.50	9.45± 0.054	2.18± 0.243
F9	0.26± 0.034	309± 5.51	12.14± 0.045	2.46± 0.109
F10	0.25± 0.023	304± 4.50	11.96± 0.091	2.00± 0.63

Performance parameters:

Content uniformity of active ingredient:

Table no.9.2 shows the result of drug content uniformity in each formulation. Three replicates of each test were carried out. The mean drug content was found to be in the range of 3.68 to 3.8 for (each patch size 10mm diameter) the prepared buccal patch formulations.

Measurement of bioadhesive strength:

An effective buccal mucosal device must maintain an intimate contact with mucus layer overlying the epithelial tissue. This parameter very important to successful utilization of these dosage forms. Hence in-vitro evaluation of buccal patches was carried out using porcine gastric mucosa. This gives the indirect measurement of bioadhesive strength in grams.

Table no9.1 represents the bioadhesive strength of the each formulation of buccal patches. The mean bioadhesive strength values were found to be 144.3, 149.34, 187.67, 176.28, 167.33, 132.64, 134.23, 167.35, 168.23 and 159.46 for F1 to F10 respectively.

Force on adhesion (N) 1.40, 1.44, 1.82, 1.62, 1.75, 1.62, 1.42, 1.47, 1.76 and 1.12 (N) for F1 to F10 respectively. Bond strength (Nm^{-2}) 453.08, 432.12, 586.09, 543.63, 513.78, 421.12, 435.47, 564.65, 523.34 and 498.21 (Nm^{-2}) for F1 to F10 respectively.

Measurement of surface P^H :

Table no9.2 shows the result of surface ph values for each formulation. These values represent the mean of three replicate determinations. They were found to be with in the range of 6.3 to 6.6 for all formulations and were almost with in the range of salivary p^H i.e. 6.2 to 7.4. It represents the better patient acceptability.

Table .no.9.1: Evaluation of Performance parameters of different mucoadhesive buccal patches of Dimenhydrinate.

Formulation code	Performance parameters(Bio adhesive)		
	Bioadhesive strength(gms) ±S.D (n=3)	Force of adhesion(N) ±S.D (n=3)	Bond strength ±S.D (n=3) (kg/mm2)
F1	144.3± 2.64	1.40± 0.03	453.02± 5.34
F2	149.34± 2.13	1.44± 0.02	432.12± 3.65
F3	187.67± 0.78	1.82± 0.05	586.09± 5.23
F4	176.28± 0.98	1.62± 0.01	543.63± 1.86
F5	167.33± 1.34	1.75± 0.01	513.78± 4.33
F6	132.64± 3.67	1.62± 0.06	421.12± 6.98
F7	134.23± 2.87	1.42± 0.04	435.47± 5.32
F8	167.35± 1.74	1.47± 0.03	564.65± 6.90
F9	168.23± 1.53	1.76± 0.01	523.34± 3.23
F10	159.46± 1.13	1.12± 0.01	498.21± 4.98

Table No.9.2: Evaluation of Performance parameters of different mucoadhesive buccal patches of Dimenhydrinate.

Formulation code	Performance parameters(Bio adhesive)		
	Drug content(mgs) ±S.D (n=3)	Surface P^H ±S.D (n=3)	Invitro residence time (min)±S.D (n=3) (kg/mm2)
F1	3.73± 0.23	6.3± 0.54	320±10
F2	3.78± 0.13	6.4± 0.43	350±5
F3	3.71± 0.011	6.6± 0.57	490± 15
F4	3.80± 0.54	6.5± 0.43	420± 5
F5	3.75± 0.36	6.4± 0.57	450±10
F6	3.69± 0.45	6.4± 0.57	310±10
F7	3.68± 0.98	6.6± 0.23	300± 10
F8	3.76± 0.21	6.3± 0.45	421± 15
F9	3.73± 0.11	6.6± 0.34	480± 5
F10	3.78± 0.78	6.4± 0.23	430± 10

In vitro release study:

The in-vitro dissolution was studied in phosphate buffer p^H 6.8. The Invitro dissolution studies were carried out in triplicate and the results shown in the tables are

mean of the replicate values. The Invitro released data obtained for patches F1 to F10 are tabulated in table no.10 to 19 respectively

The results of Invitro dissolution studies obtained in these formulations were floated in 4 models of data treatments as follows

1. Cumulative percentage of drug released Vs time. (Zero order)

2. Log cumulative percentage of drug retained Vs time. (First order)

3. Cumulative percentage of drug released Vs square root of time. (Higuchi's plot)

4. Log cumulative percentage of drug released Vs log of time. (Peppa's plot)

Graph shows the plot of cumulative percentage of drug released as a function of time for different buccal patches. Cumulative percentage drug released as found to be 99.78% (8 hours), 99.58% (7 hours), 99.49% (10 hours), 100.17 (9 hours), 100.18% (9 hours), 97.15% (8 hours), 98.54% (8 hours), 100.75% (10 hours), 99.67% (9 hours) and 100.6% (9 hours) for F1 to F10 respectively. The plot for cumulative percentage drug release verses time for all formulations are shown in graph no 6 to 24, and comparative cumulative release shown in graph no. 26.

Stability study:

Stability studies of the prepared buccal patches were carried out, by storing formulations F5 at, room temperature and humidity and 40^0 C+ 2^0C/75%RH + 5% RH in humidity control oven for ninety days. Stability studies were carried out to predict the degradation that may occur over prolonged periods of storage at various temperatures and humidity for formulations F5 over a period of 90 days. The results of the stability studies, which were conducted for 90 days, are shown in table no.24. The result obtained showed a slight decrease in, in vitro release of formulations F5 as compared to the fresh formulations F5. The shelf life of the fabricated device was calculated based on these parameters.

Kinetic study:

To study the drug release kinetics, data obtained from In-Vitro drug release studies are plotted in various kinetic models.

i) Zero order:

It is plotted as cumulative amount of drug released Vs time.

$$C=K_0 t$$

Where K_0 is the zero order rate constant expressed in units of concentration by time.

T is the time in hours.

A graph of concentration Vs time would yield a straight line with a slope equal to k_0 and the intercept at the origin of the axis.

ii) First order:

It is plotted as log cumulative percentage of drug remaining Vs time.

$$LogC = LogC_0 – Kt/2.303$$

Where Co is the initial concentration of drug, K is the first order constant, t is the time in hours.

iii) Higuchi model:

It is plotted as cumulative percentage of drug release Vs square root of time.

$$Q=Kt^{1/2}$$

Where K is the constant reflecting the design variables of the system, t is the time in hours.

Hence, release rate is proportional to the reciprocal of square root of time t.

iv) Korsmeyer and Peppa's:

As log cumulative percentage of drug released Vs square root of time, and the exponent n is calculated through the slope of the straight line.

$$M_t/M_\infty= Kt^n$$

Where M_t/M_∞ is the fractional solute release, T is the release time, K is a kinetic constant characteristic of the drug/polymer system and is an exponent that characterizes the mechanism of release of tracers

The slope n was computed to know whether the release was Fickian or Non-Fickian. For Non-Fickian release the n values falls between 0.5 and 1.0 , while for Fickian diffusion n is less than or equal to 0.5. The slope values are tabulated in table no.22. The values of n were more than 0.5 for all formulations.

Table no. 6 Diffusional n values

N	Mechanism
0.5	Fickian diffusion
0.5<n<1	Non-Fickian diffusion
1	Case II transport

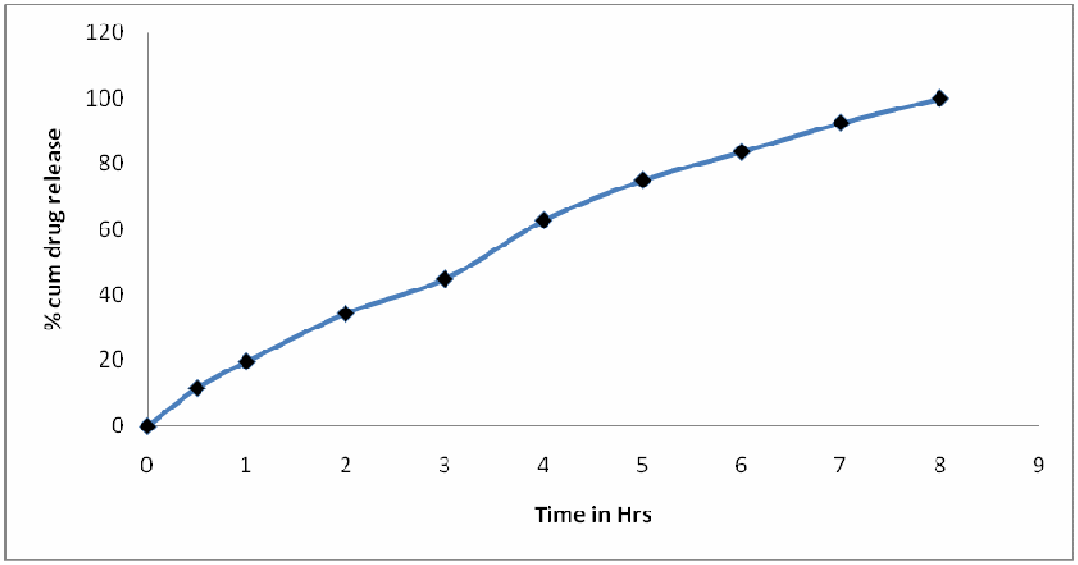
n is the Diffusional exponent and is also an important indicator of transport of drug through the polymer.

The model fitting graphs for each formulation are shown in graph no.7 to 25.

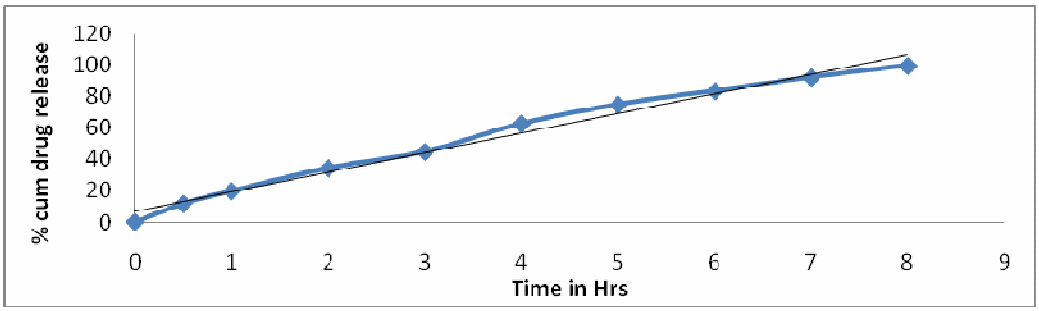
Table No.10: Invitro Drug Release of mucoadhesive buccal patches of DimenhydrinateF1

Time in hrs	Log time	SQ.RT of time	Abs (276nm)	Cum% release	Log cum% release
0	0.000	0.000	0.000	0.000	0.000
0.5	-0.301	0.707	0.016	11.59	1.064
1	0.000	1.000	0.027	19.67	1.294
2	0.301	1.414	0.047	34.36	1.536
3	0.477	1.732	0.061	44.85	1.651
4	0.602	2.000	0.085	62.68	1.797
5	0.698	2.236	0.101	74.89	1.874
6	0.778	2.449	0.112	83.59	1.922
7	0.845	2.645	0.123	92.37	1.965
8	0.903	2.828	0.132	99.78	1.999

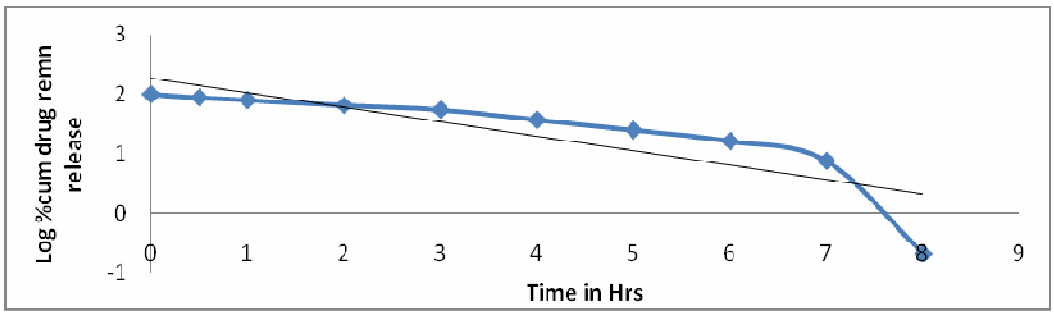
Graph No.6: Dissolution profile for Formulation F1



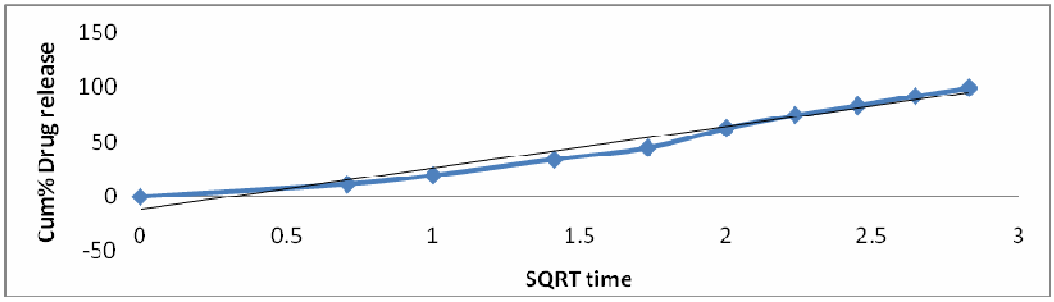
Graph No.7: (a) Zero order Drug Release Kinetics for Formulation F1



(a) First order Drug Release Kinetics for Formulation F1



(a) Higuchi's Drug Release Kinetics for Formulation F1



(D) Korsmeyer-Peppa's Drug Release Kinetics for Formulation F1

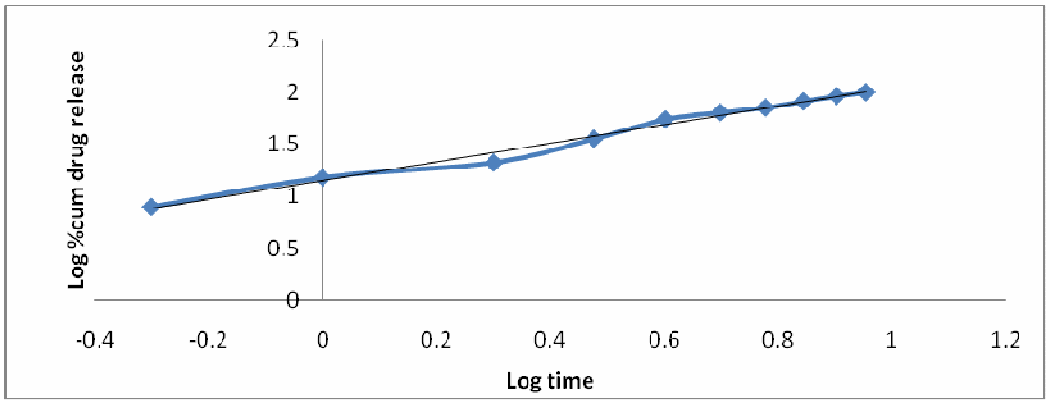
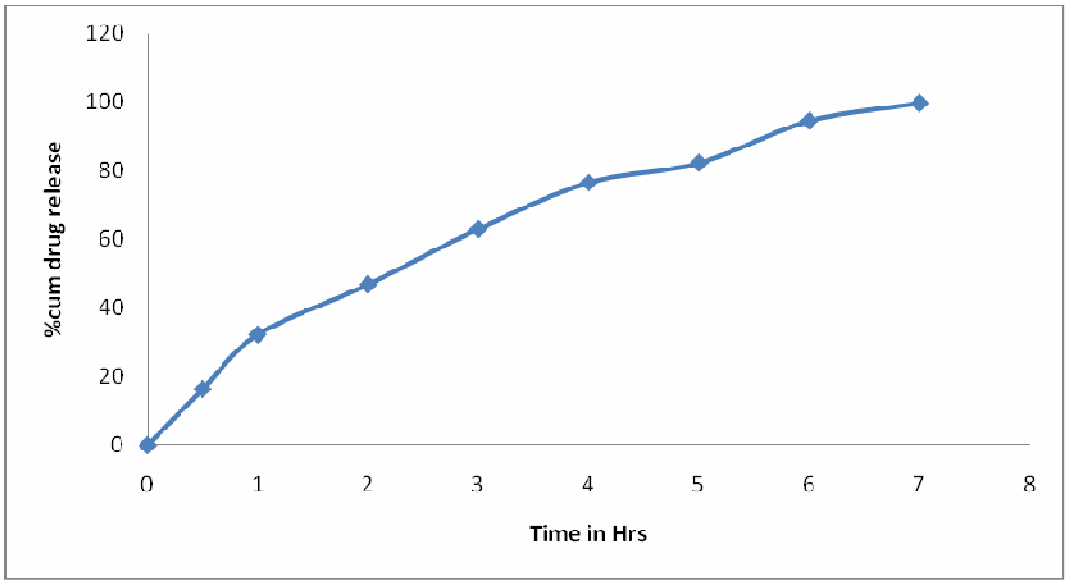


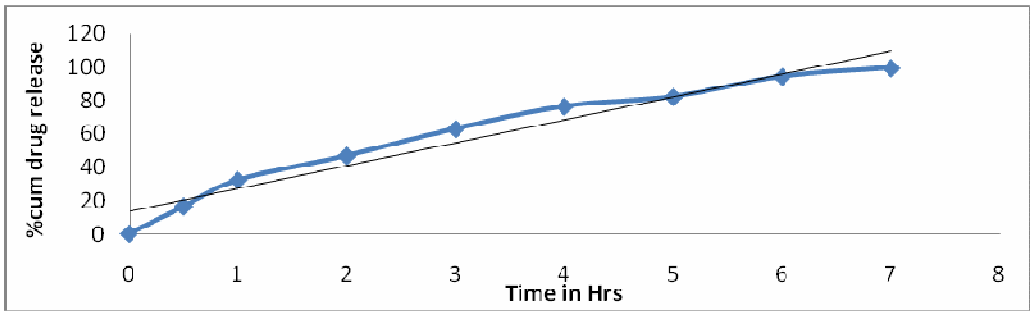
Table. No.11: Invitro Drug Release of mucoadhesive buccal patches of DimenhydrinateF2

Time in hrs	Log time	SQ.RT of time	Abs (276nm)	Cum% release	Log cum% release
0	0.000	0.000	0.000	0.000	0.000
0.5	-0.301	0.707	0.023	16.4	1.214
1	0.000	1.000	0.045	32.25	1.508
2	0.301	1.414	0.065	46.83	1.670
3	0.477	1.732	0.087	62.98	1.799
4	0.602	2.000	0.105	76.44	1.883
5	0.698	2.236	0.112	82.18	1.914
6	0.778	2.449	0.128	94.39	1.974
7	0.845	2.645	0.134	99.58	1.998

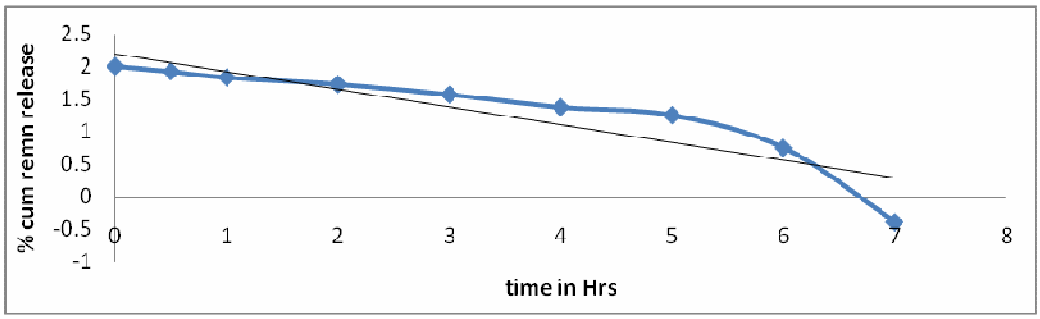
Graph No.8: Dissolution profile for Formulation F2



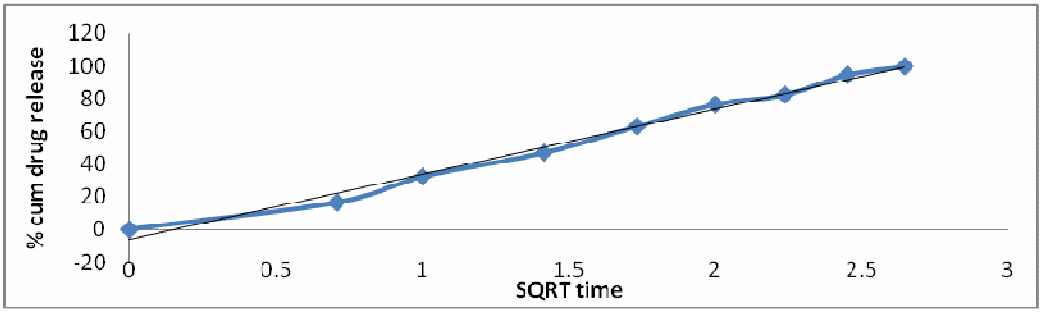
Graph No.9: (a) Zero order Drug Release Kinetics for Formulation F2



(b) First order Drug Release Kinetics for Formulation F2



(c) Higuchi's Drug Release Kinetics for Formulation F2



(D) Korsmeyer-Peppa's Drug Release Kinetics for Formulation F2

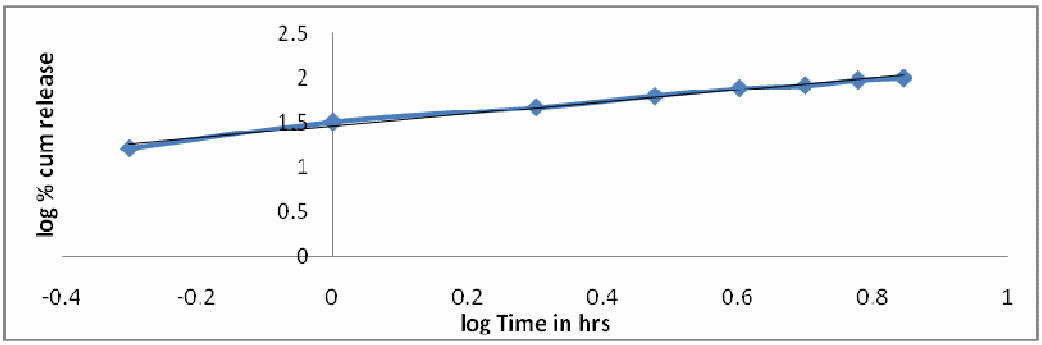
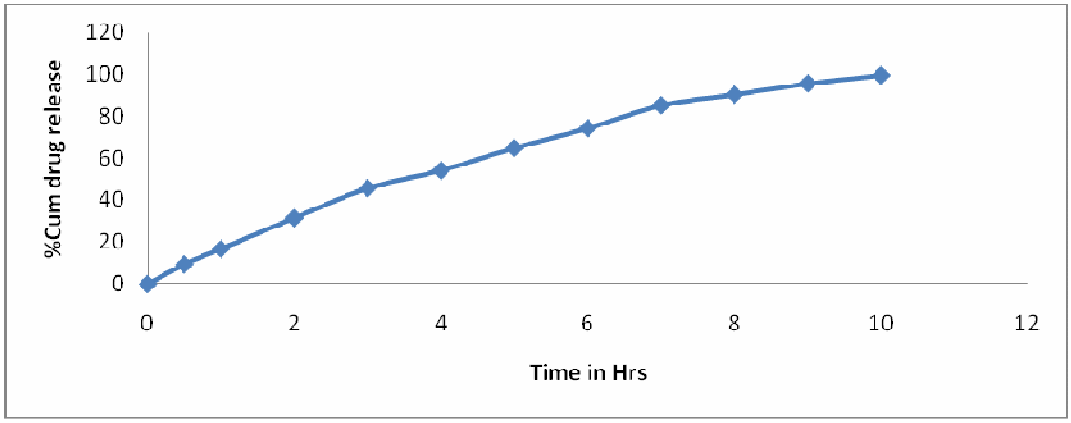


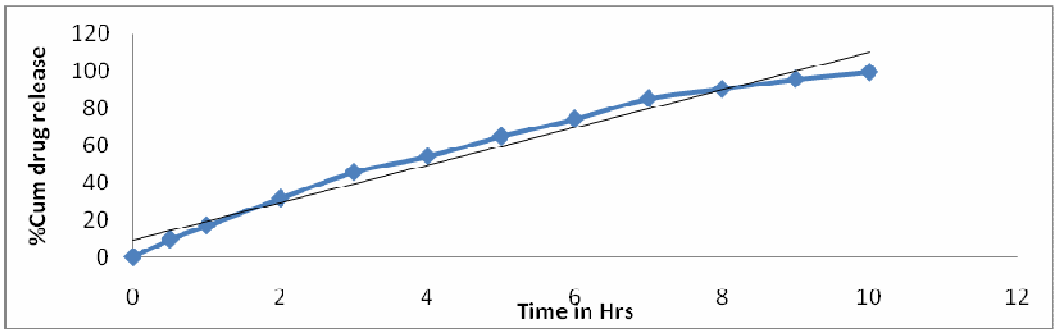
Table No.12: Invitro Drug Release of mucoadhesive buccal patches of DimenhydrinateF3

Time in hrs	Log time	SQ.RT of time	Abs (276nm)	Cum% release	Log cum% release
0	0.000	0.000	0.000	0.000	0.000
0.5	-0.301	0.707	0.013	9.47	0.976
1	0.000	1.000	0.023	16.85	1.226
2	0.301	1.414	0.043	31.58	1.499
3	0.477	1.732	0.062	45.74	1.660
4	0.602	2.000	0.073	54.20	1.734
5	0.698	2.236	0.087	64.93	1.812
6	0.778	2.449	0.099	74.31	1.871
7	0.845	2.645	0.113	85.23	1.930
8	0.903	2.828	0.119	90.42	1.956
9	0.954	3.000	0.125	95.66	1.980
10	1	3.162	0.129	99.49	1.998

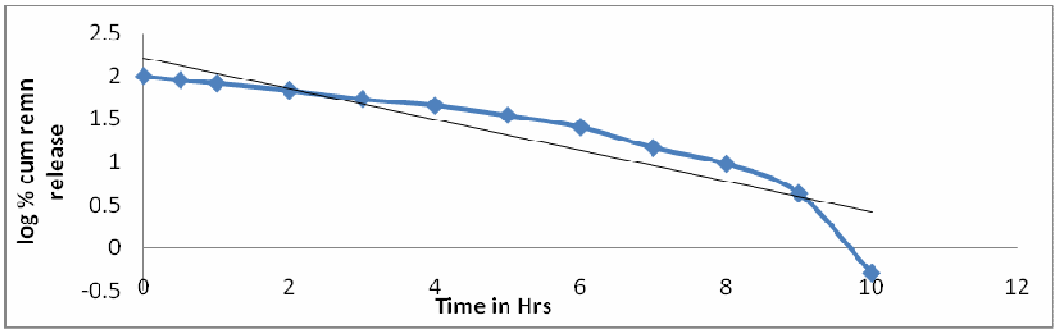
Graph No.10: Dissolution profile for Formulation F3



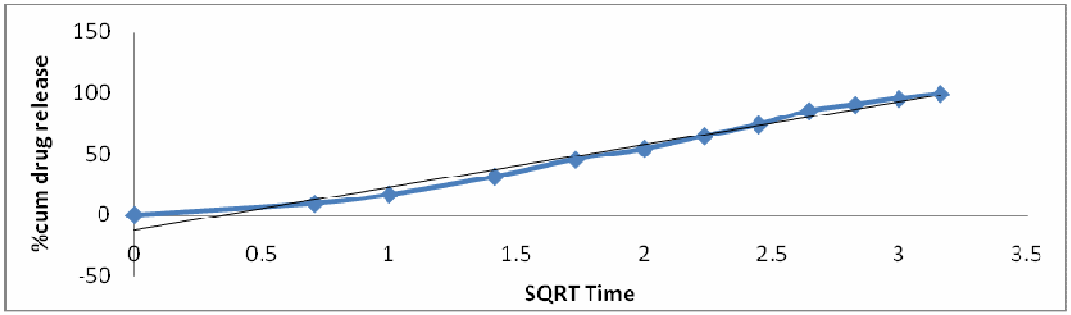
Graph No.11: (a) Zero order Drug Release Kinetics for Formulation F3



(b) First order Drug Release Kinetics for Formulation F3



(C) Higuchi's Drug Release Kinetics for Formulation F3



(D) Korsmeyer-Peppa's Drug Release Kinetics for Formulation F3

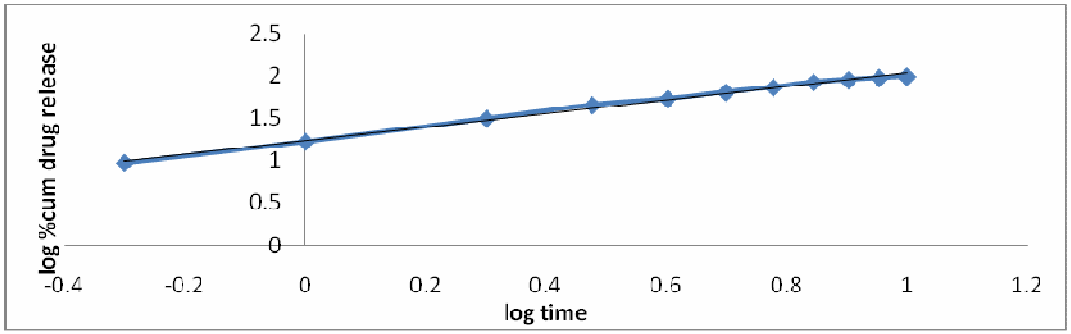
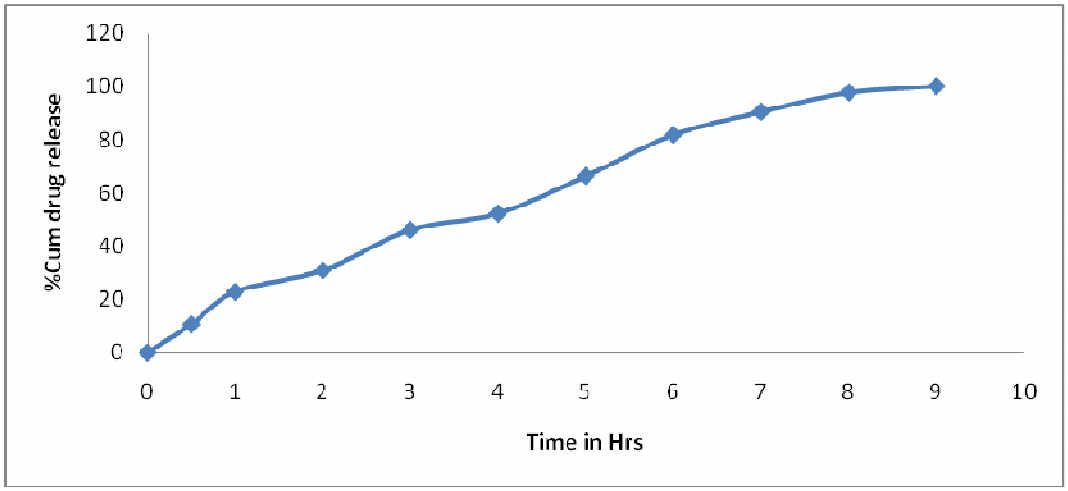


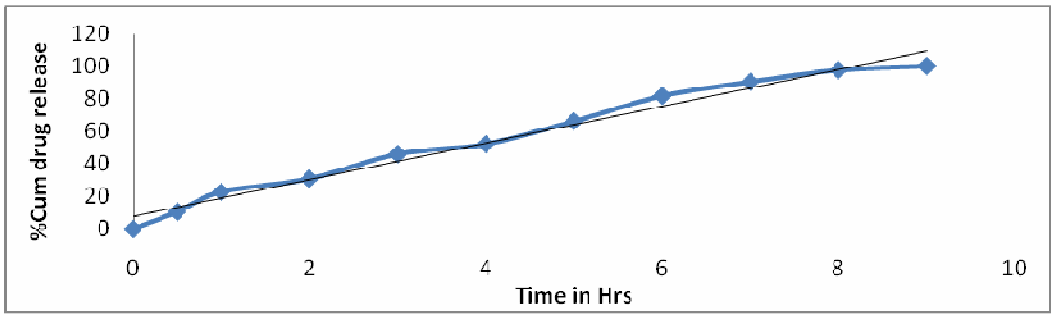
Table No.13: Invitro Drug Release of mucoadhesive buccal patches of DimenhydrinateF4

Time in hrs	Log time	SQ.RT of time	Abs (276nm)	Cum% release	Log cum% release
0	0.000	0.000	0.000	0.000	0.000
0.5	-0.301	0.707	0.015	10.66	1.028
1	0.000	1.000	0.032	22.86	1.359
2	0.301	1.414	0.043	30.91	1.490
3	0.477	1.732	0.064	46.15	1.664
4	0.602	2.000	0.072	52.30	1.718
5	0.698	2.236	0.091	66.33	1.821
6	0.778	2.449	0.112	81.91	1.913
7	0.845	2.645	0.123	90.53	1.956
8	0.903	2.828	0.132	97.8	1.990
9	0.9542	3	0.135	100.17	2.000

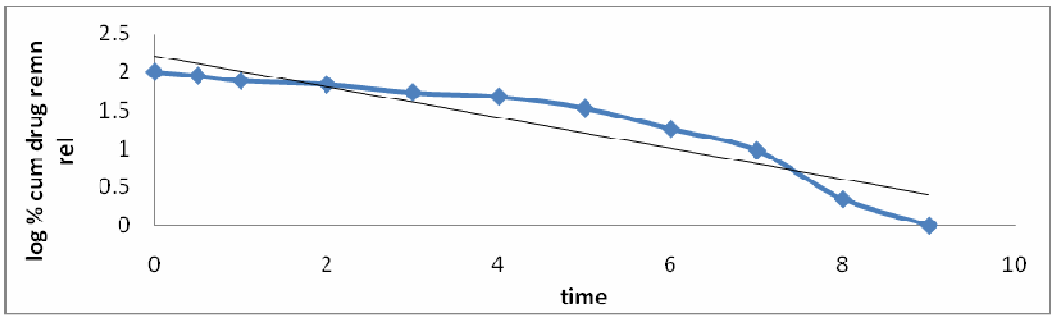
Graph No.12: Dissolution profile for Formulation F4



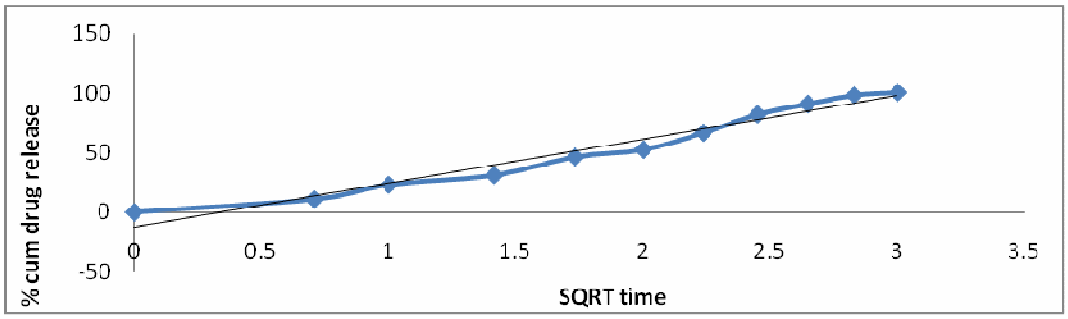
Graph No.13: (a) Zero order Drug Release Kinetics for Formulation F4



(a) First order Drug Release Kinetics for Formulation F4



(a) Higuchi's Drug Release Kinetics for Formulation F4



(D) Korsmeyer-Peppa's Drug Release Kinetics for Formulation F4

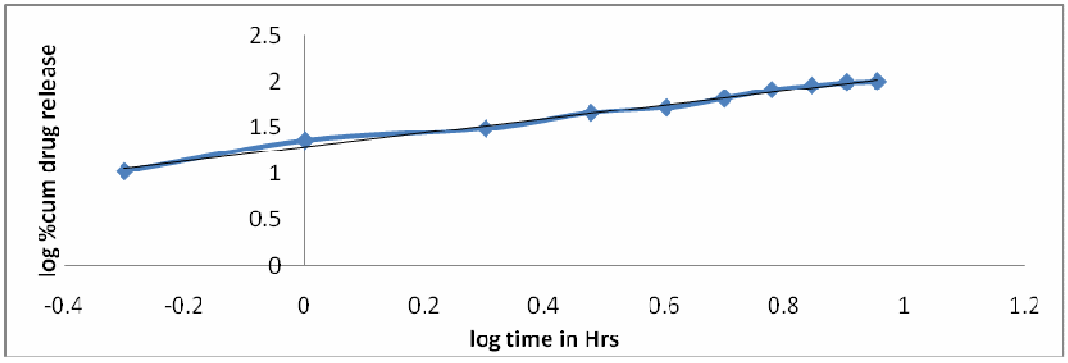
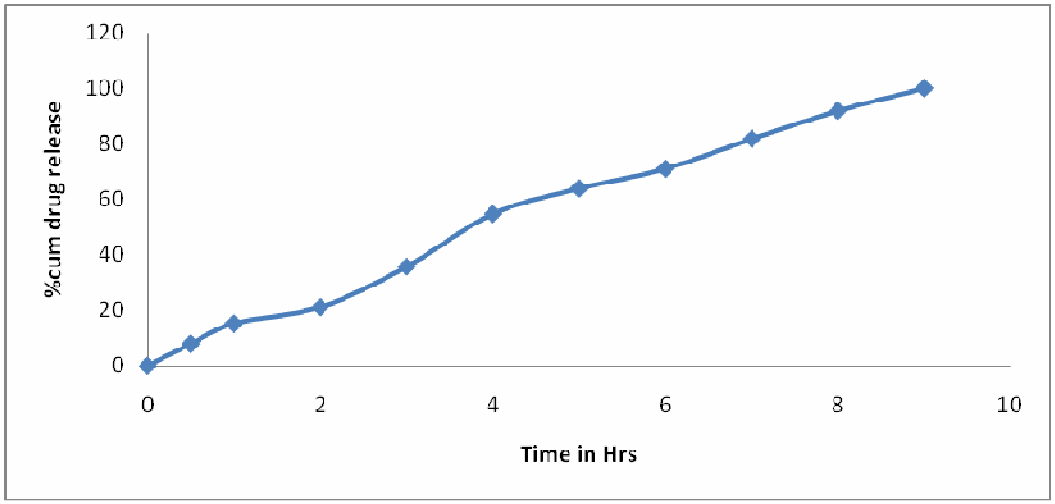


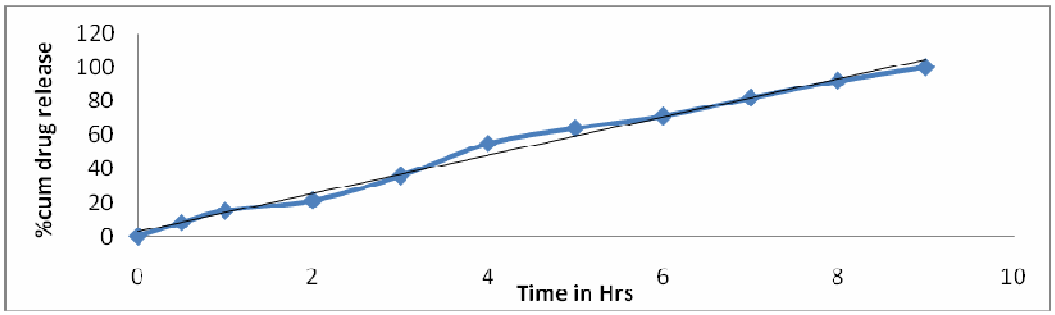
Table. No.14: Invitro Drug Release of mucoadhesive buccal patches of DimenhydrinateF5

Time in hrs	Log time	SQ.RT of time	Abs (276nm)	Cum% release	Log cum% release
0	0.000	0.000	0.000	0.000	0.000
0.5	-0.301	0.707	0.011	7.92	0.899
1	0.000	1.000	0.021	15.21	1.182
2	0.301	1.414	0.029	21.13	1.324
3	0.477	1.732	0.049	35.75	1.553
4	0.602	2.000	0.075	54.84	1.739
5	0.698	2.236	0.087	64.03	1.806
6	0.778	2.449	0.096	71.14	1.852
7	0.845	2.645	0.110	81.93	1.913
8	0.903	2.828	0.123	92.09	1.964
9	0.954	3.000	0.133	100.18	2.000

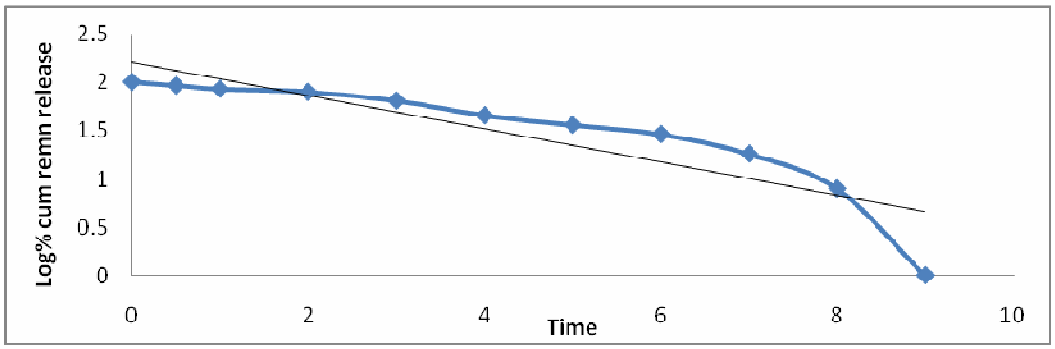
Graph No.14: Dissolution profile for Formulation F5



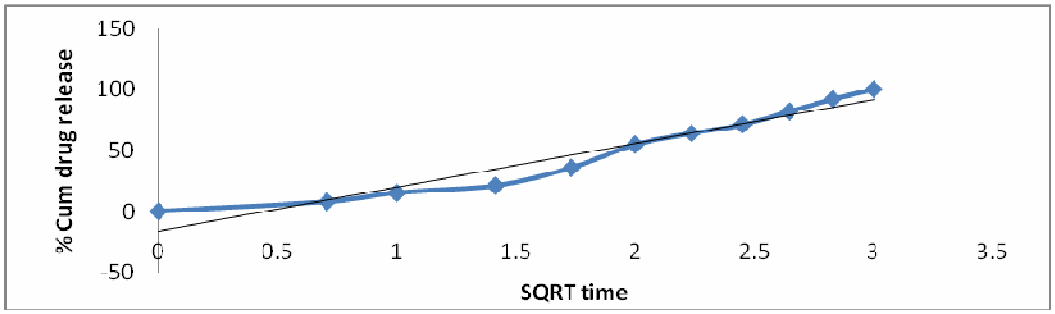
Graph No.15: (a) Zero order Drug Release Kinetics for Formulation F5



(b) First order Drug Release Kinetics for Formulation F5



(a) Higuchi's Drug Release Kinetics for Formulation F5



(D) Korsmeyer-Peppa's Drug Release Kinetics for Formulation F5

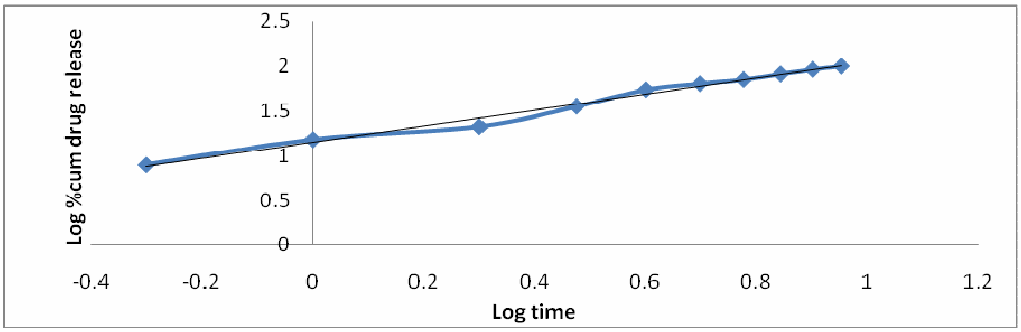
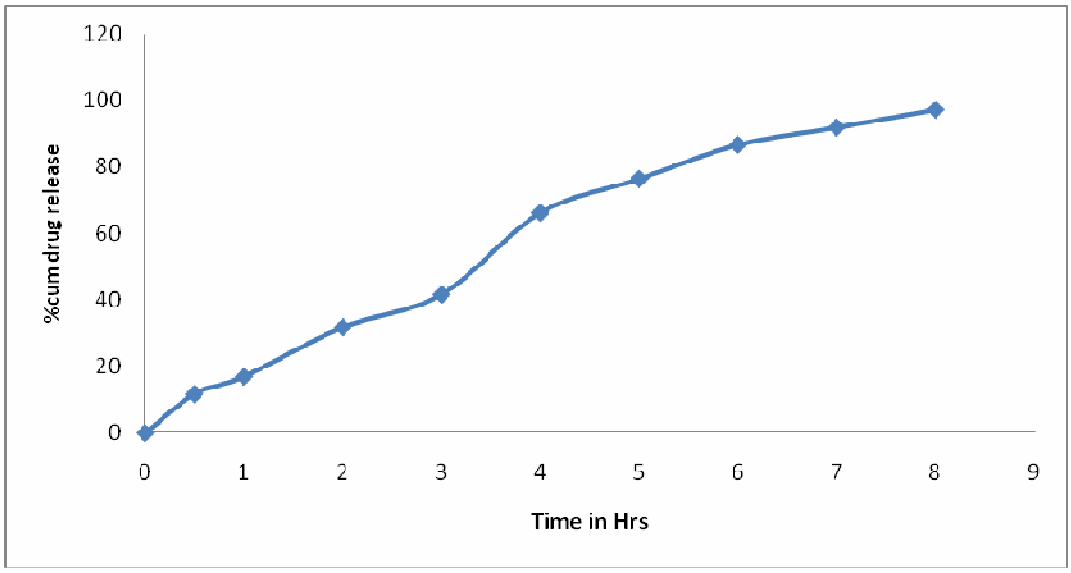


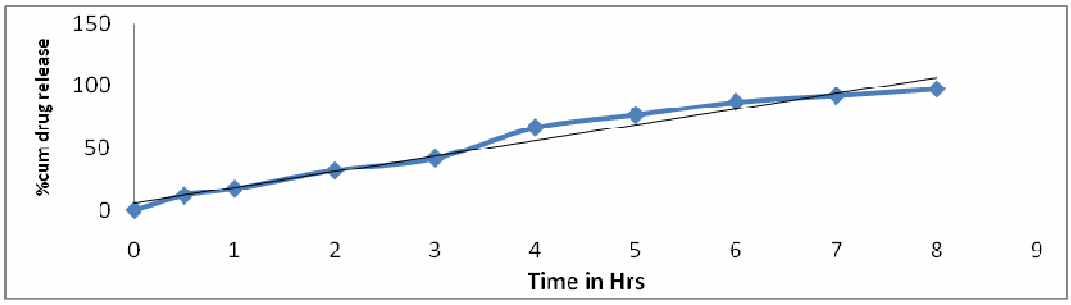
Table. No.15: Invitro Drug Release of mucoadhesive buccal patches of DimenhydrinateF6

Time in hrs	Log time	SQ.RT of time	Abs (276nm)	Cum% release	Log cum% release
0	0.000	0.000	0.000	0.000	0.000
0.5	-0.301	0.707	0.016	11.71	1.068
1	0.000	1.000	0.023	16.96	1.229
2	0.301	1.414	0.043	31.78	1.502
3	0.477	1.732	0.056	41.61	1.619
4	0.602	2.000	0.089	66.19	1.820
5	0.698	2.236	0.102	76.37	1.882
6	0.778	2.449	0.115	86.64	1.937
7	0.845	2.645	0.121	92.87	1.963
8	0.903	2.828	0.127	99.15	1.987

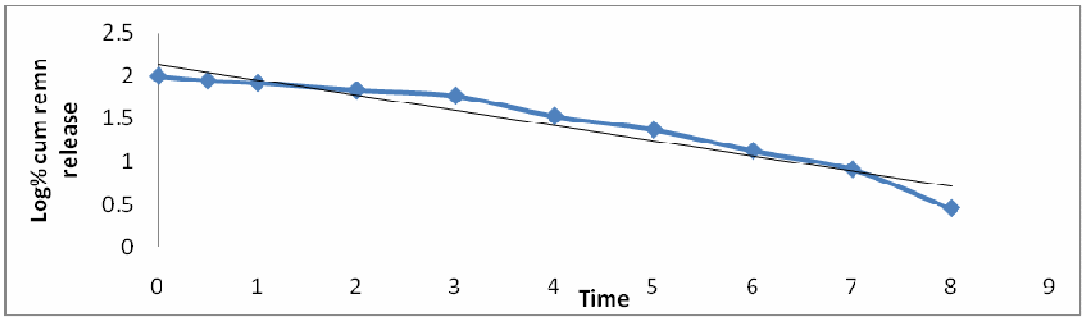
Graph No.16: Dissolution profile for Formulation F6



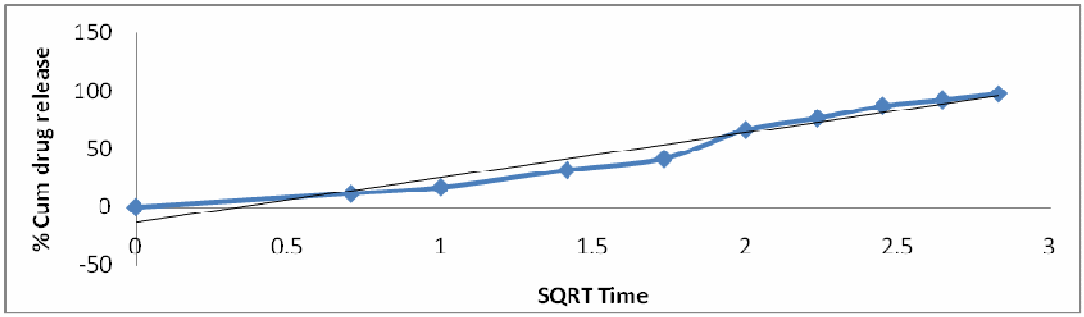
Graph No.17: (a) Zero order Drug Release Kinetics for Formulation F6



(a) First order Drug Release Kinetics for Formulation F6



(c) Higuchi's Drug Release Kinetics for Formulation F6



(d) Korsmeyer-Peppa's Drug Release Kinetics for Formulation F6

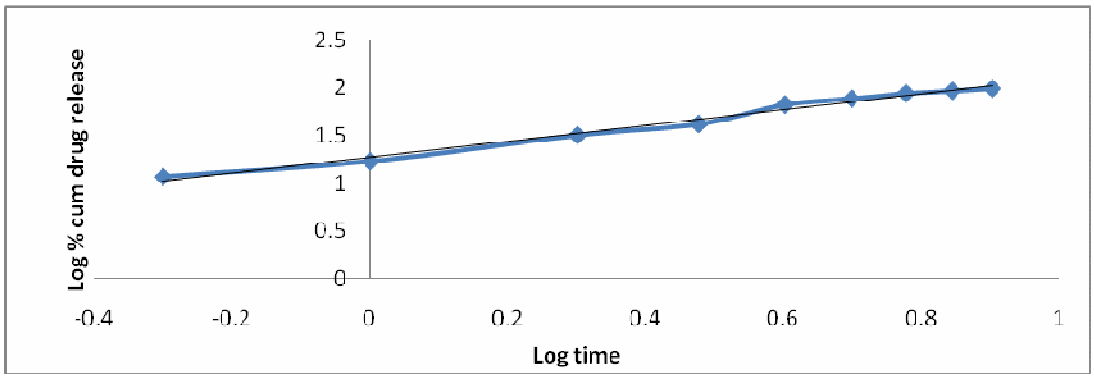
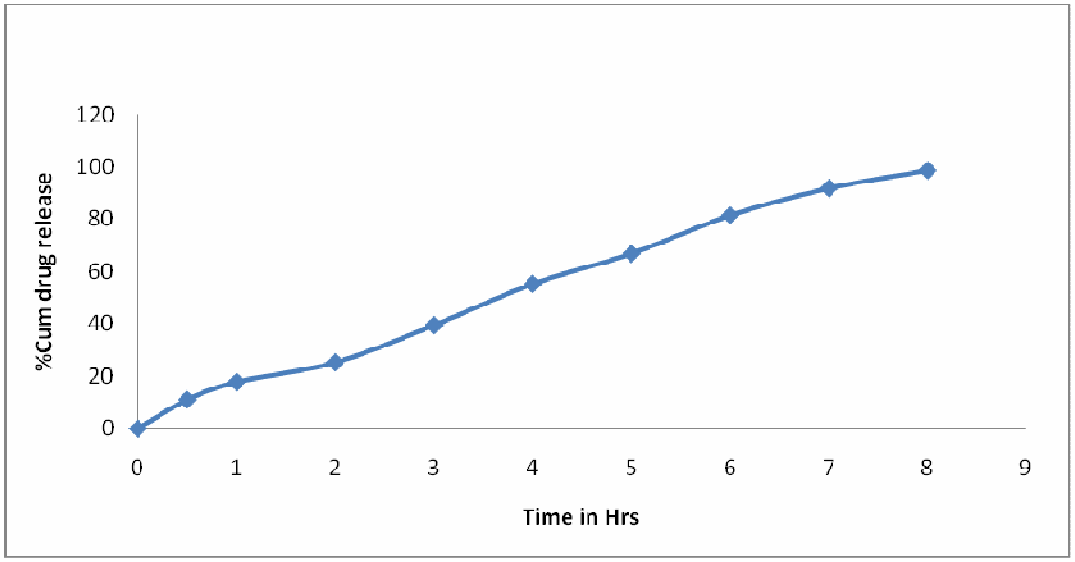


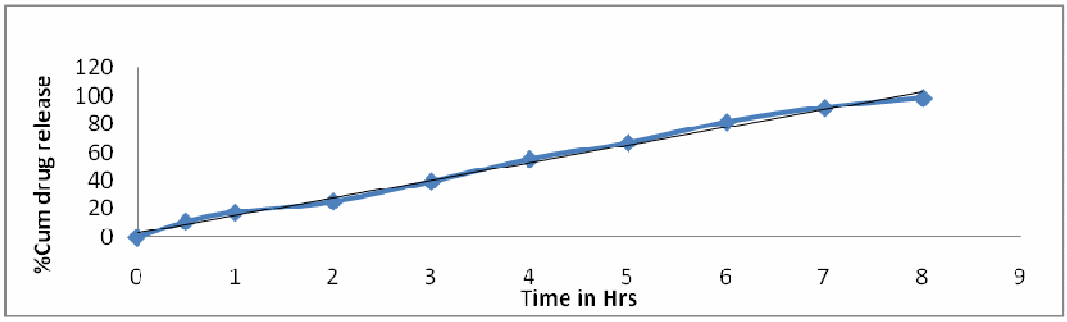
Table. No.16: Invitro Drug Release of mucoadhesive buccal patches of DimenhydrinateF7

Time in hrs	Log time	SQ.RT of time	Abs (276nm)	Cum% release	Log cum% release
0	0.000	0.000	0.000	0.000	0.000
0.5	-0.301	0.707	0.015	11.01	1.042
1	0.000	1.000	0.024	17.73	1.248
2	0.301	1.414	0.034	25.25	1.402
3	0.477	1.732	0.053	39.46	1.596
4	0.602	2.000	0.074	55.27	1.742
5	0.698	2.236	0.089	66.83	1.824
6	0.778	2.449	0.108	81.44	1.910
7	0.845	2.645	0.121	91.78	1.962
8	0.903	2.828	0.129	98.54	1.993

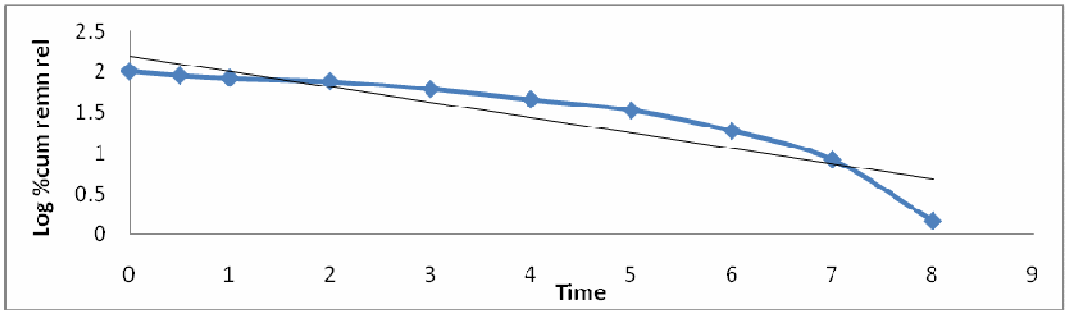
Graph No.18: Dissolution profile for Formulation F7



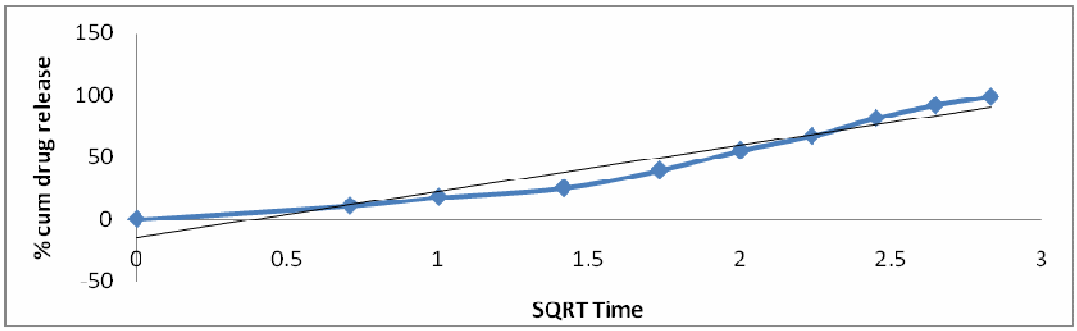
Graph No.19: (a) Zero order Drug Release Kinetics for Formulation F7



(b) First order Drug Release Kinetics for Formulation F7



(c) Higuchi's Drug Release Kinetics for Formulation F7



(D) Korsmeyer-Peppa's Drug Release Kinetics for Formulation F7

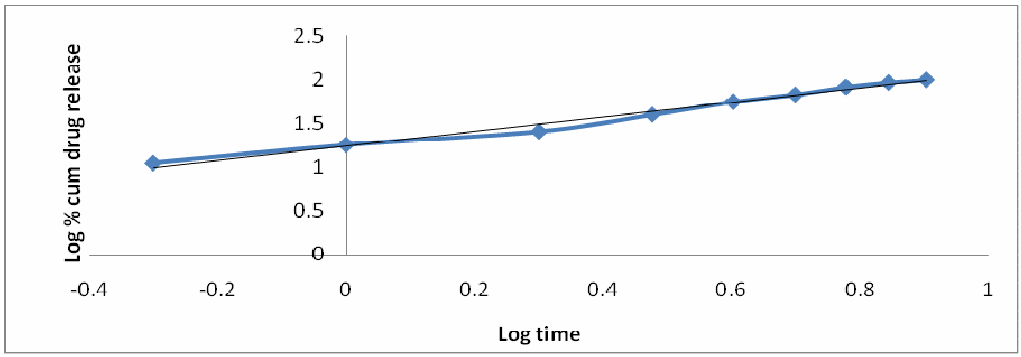
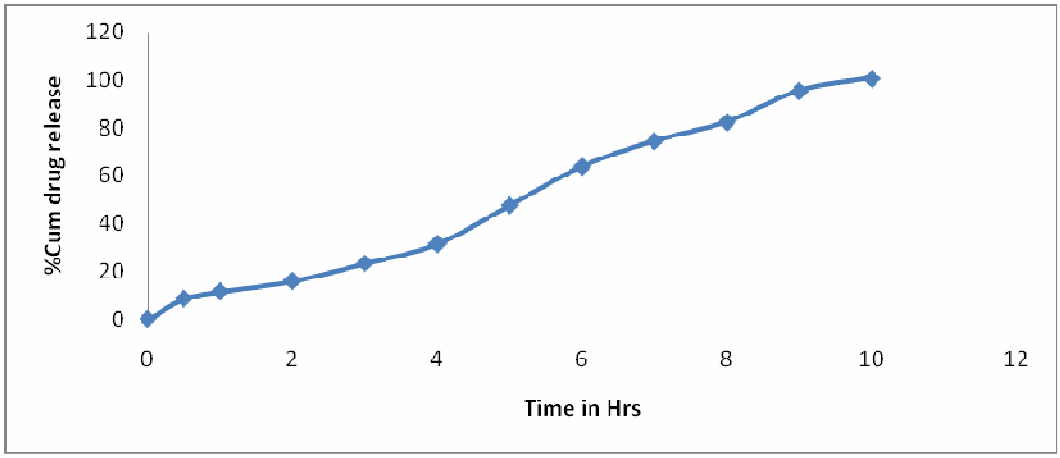


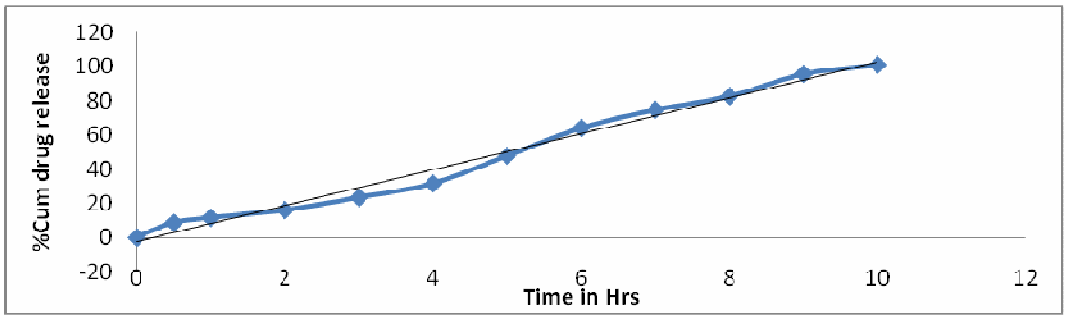
Table No.18: Invitro Drug Release of mucoadhesive buccal patches of DimenhydrinateF8

Time in hrs	Log time	SQ.RT of time	Abs (276nm)	Cum% release	Log cum% release
0	0.000	0.000	0.000	0.000	0.000
0.5	-0.301	0.707	0.012	8.62	0.935
1	0.000	1.000	0.016	11.58	1.063
2	0.301	1.414	0.022	16.01	1.204
3	0.477	1.732	0.032	23.36	1.368
4	0.602	2.000	0.043	31.49	1.498
5	0.698	2.236	0.065	47.62	1.677
6	0.778	2.449	0.087	63.90	1.805
7	0.845	2.645	0.101	74.59	1.872
8	0.903	2.828	0.111	82.50	1.916
9	0.954	3.000	0.128	95.52	1.980
10	1	3.162	0.136	100.75	2.003

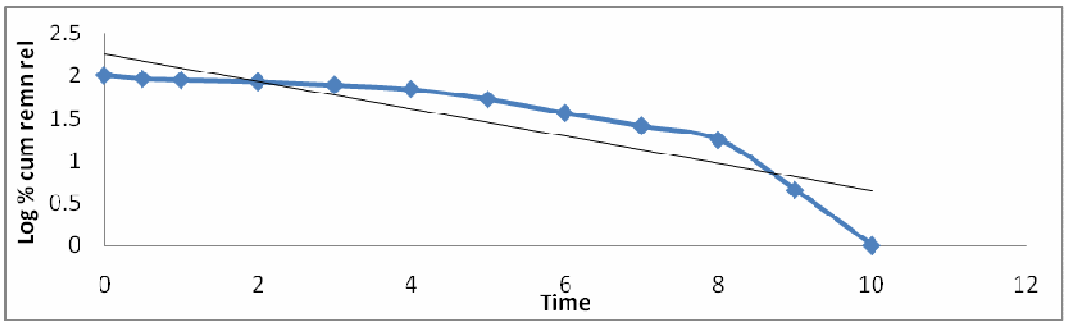
Graph No.20: Dissolution profile for Formulation F8



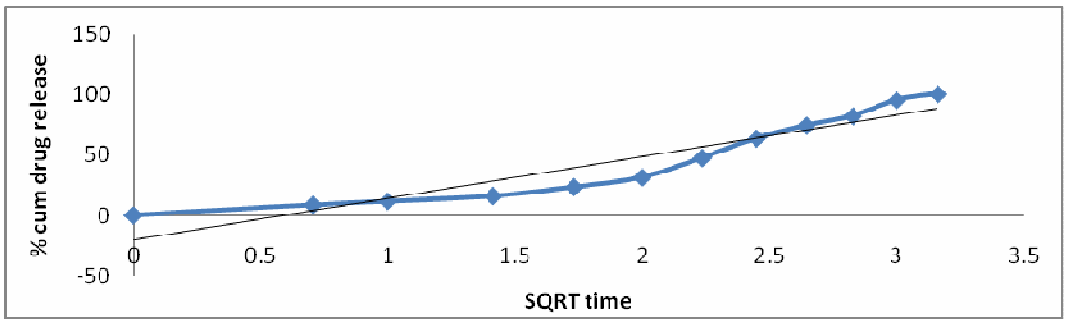
Graph No.21: (a) Zero order Drug Release Kinetics for Formulation F8



(b) First order Drug Release Kinetics for Formulation F8



(c) Higuchi's Drug Release Kinetics for Formulation F8



(D) Korsmeyer-Peppa's Drug Release Kinetics for Formulation F8

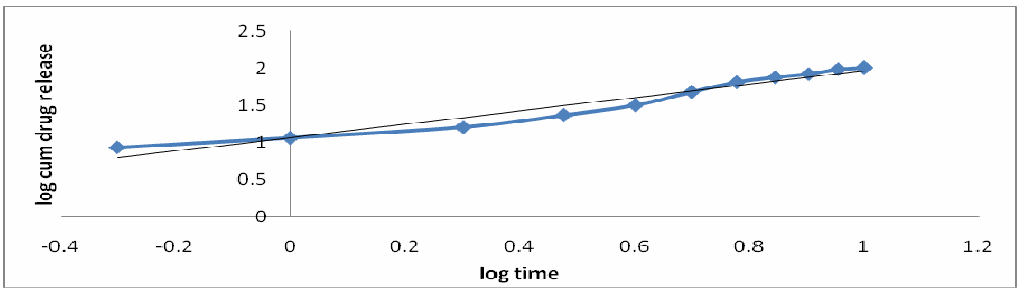
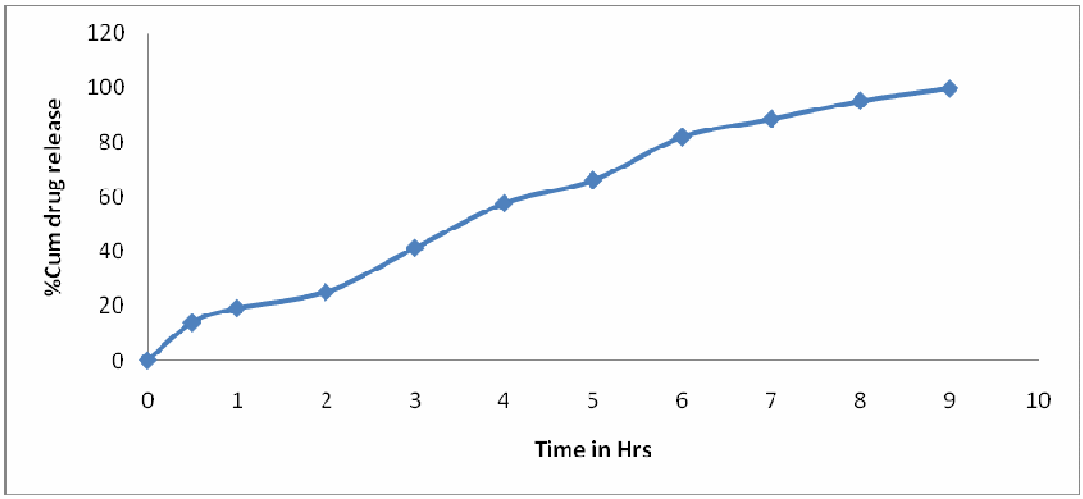


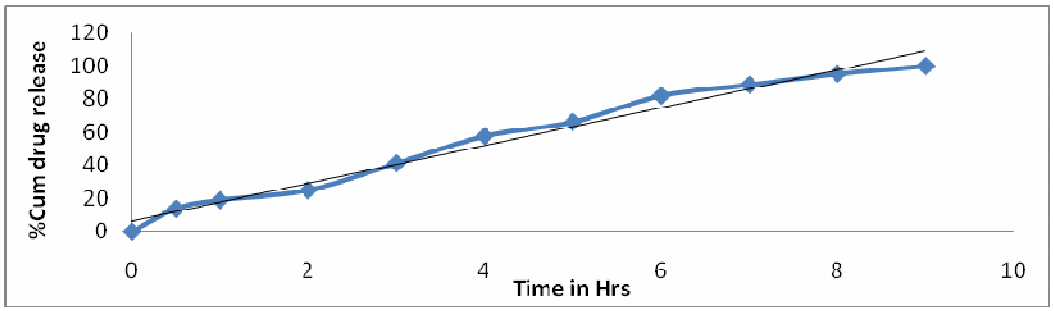
Table No.19: Invitro Drug Release of mucoadhesive buccal patches of DimenhydrinateF9

Time in hrs	Log time	SQ.RT of time	Abs (276nm)	Cum% release	Log cum% release
0	0.000	0.000	0.000	0.000	0.000
0.5	-0.301	0.707	0.019	13.76	1.138
1	0.000	1.000	0.026	18.97	1.278
2	0.301	1.414	0.034	24.96	1.397
3	0.477	1.732	0.056	41.14	1.614
4	0.602	2.000	0.078	57.49	1.759
5	0.698	2.236	0.089	66.03	1.819
6	0.778	2.449	0.110	81.89	1.913
7	0.845	2.645	0.118	88.48	1.946
8	0.903	2.828	0.126	95.13	1.978
9	0.954	3.000	0.131	99.67	1.998

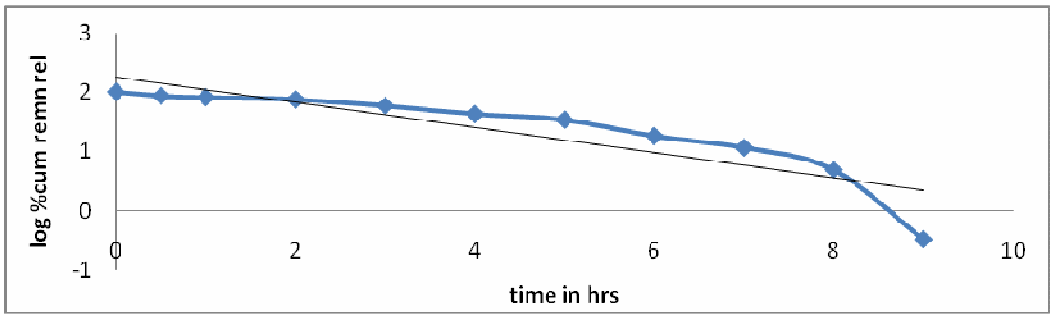
Graph No.22: Dissolution profile for Formulation F9



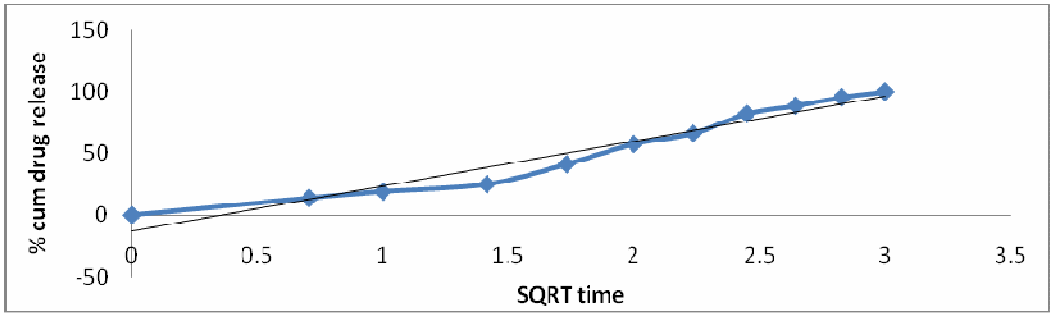
Graph No.23: (a) Zero order Drug Release Kinetics for Formulation F9



(b) First order Drug Release Kinetics for Formulation F9



(c) Higuchi's Drug Release Kinetics for Formulation F9



(D) Korsmeyer-Peppa's Drug Release Kinetics for Formulation F9

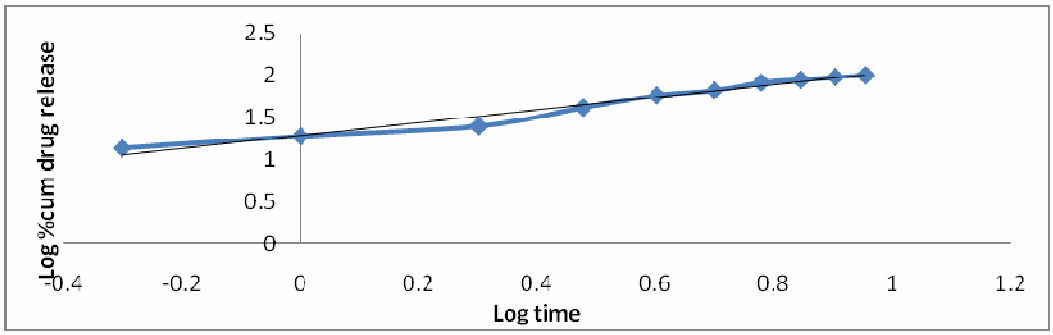
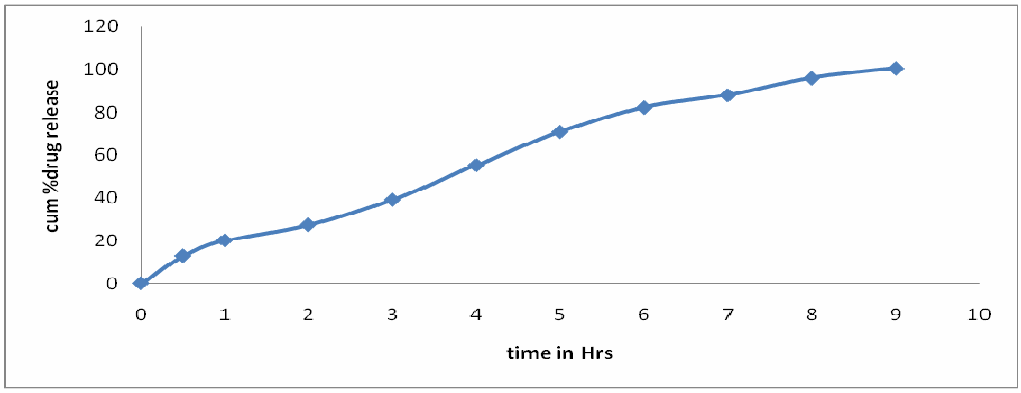


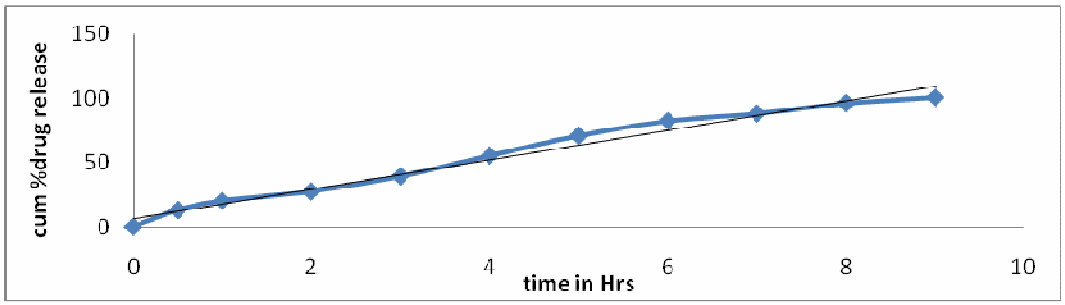
Table. No.19: Invitro Drug Release of mucoadhesive buccal patches of DimenhydrinateF10

Time in hrs	Log time	SQ.RT of time	Abs (276nm)	Cum% release	Log cum% release
0	0.000	0.000	0.000	0.000	0.000
0.5	-0.301	0.707	0.017	12.87	1.109
1	0.000	1.000	0.028	20.14	1.304
2	0.301	1.414	0.038	27.49	1.439
3	0.477	1.732	0.054	39.21	1.593
4	0.602	2.000	0.076	55.32	1.742
5	0.698	2.236	0.097	70.88	1.850
6	0.778	2.449	0.112	82.30	1.915
7	0.845	2.645	0.119	88.10	1.945
8	0.903	2.828	0.129	96.11	1.982
9	0.954	3	0.134	100.60	2.002

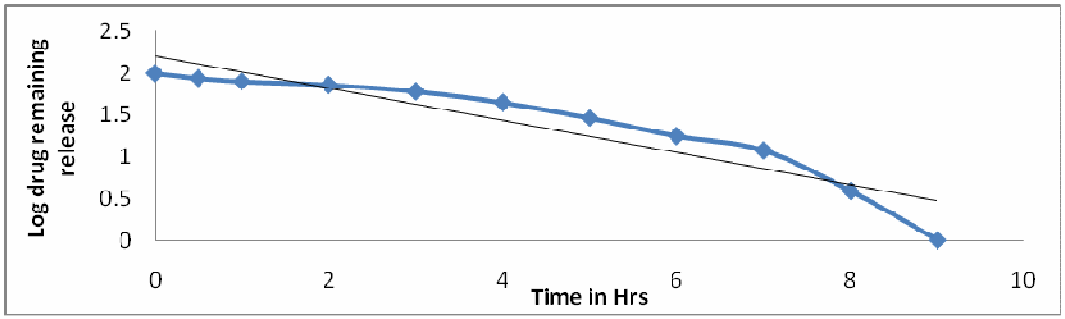
Graph No.24: Dissolution profile for Formulation F10



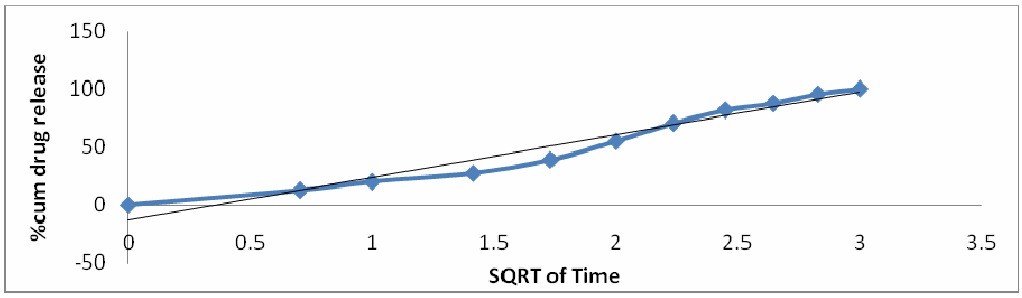
Graph. No. 25: (a) Zero order Drug Release Kinetics for Formulation F10



(b) First order Drug Release Kinetics for Formulation F10



(c) Higuchi's Drug Release Kinetics for Formulation F10



(D) Korsmeyer-Peppa's Drug Release Kinetics for Formulation F10

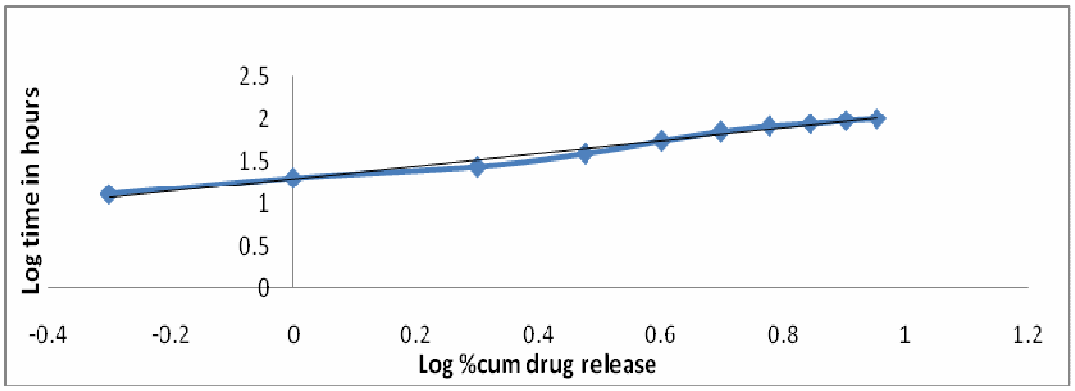


Table No. 20: Cumulative % Drug release of Formulation F1 to F10.

Time Hrs	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.5	11.59	16.4	9.47	10.66	7.92	11.71	11.01	8.62	13.76	12.87
1	19.67	32.25	16.85	22.86	15.21	16.96	17.73	11.58	18.97	20.14
2	34.36	46.83	31.58	30.91	21.13	31.78	25.25	16.01	24.96	27.49
3	44.85	62.98	45.74	46.15	35.75	41.61	39.46	23.36	41.14	39.21
4	62.68	76.44	54.20	52.30	54.84	66.19	55.27	31.49	57.49	55.32
5	74.89	82.18	64.93	66.33	64.03	76.37	66.83	47.62	66.03	70.88
6	83.59	94.39	74.31	81.91	71.14	86.64	81.44	63.90	81.89	82.30
7	92.37	99.58	85.23	90.53	81.93	92.87	91.78	74.59	88.48	88.10
8	99.78		90.42	97.8	92.09	99.15	98.54	82.50	95.13	96.11
9			95.66	100.17	100.18			95.52	99.67	100.60
10			99.49					100.75		

Graph.No.26: Comparative drug release profile for formulation F1 to F10

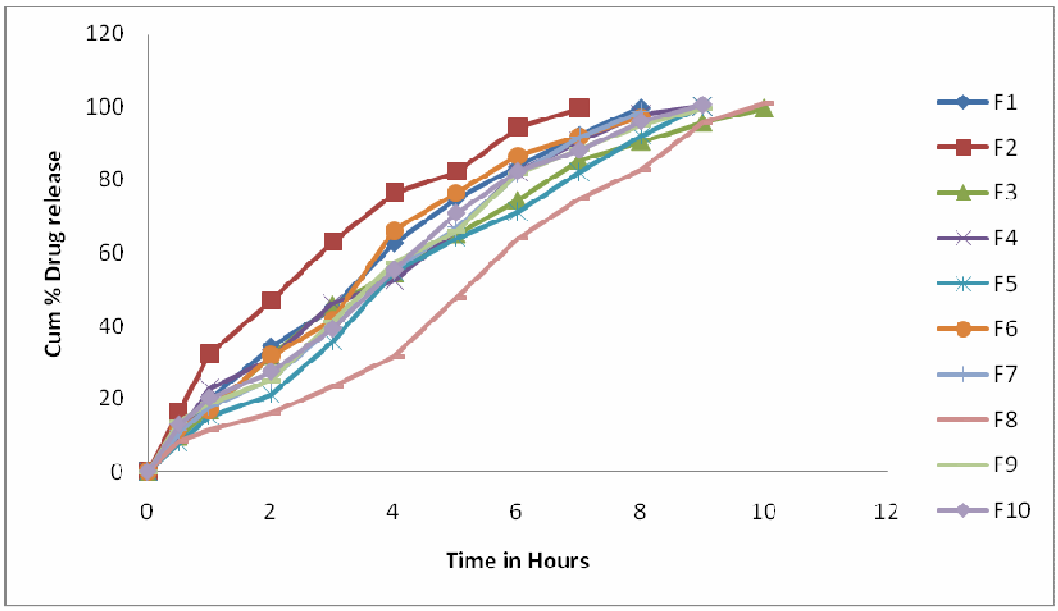
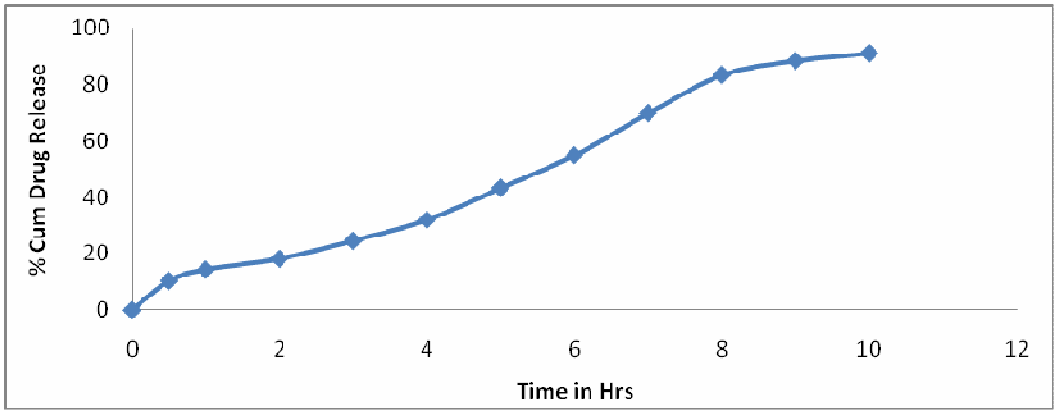


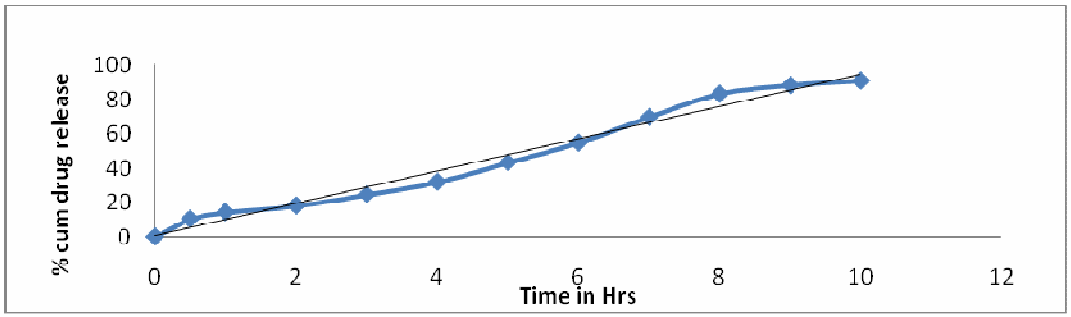
Table No.21: Ex-vivo Drug release of Mucoadhesive Buccal patches of Dimenhydrinate (F3) with Porcine Buccal mucosa.

Time in hrs	Log time	SQ.RT of time	Abs (276nm)	Cum% release	Log cum% release
0	0.000	0.000	0.000	0.000	0.000
0.5	-0.301	0.707	0.072	10.37	0.935
1	0.000	1.000	0.098	14.33	1.063
2	0.301	1.414	0.123	18.21	1.204
3	0.477	1.732	0.165	24.62	1.368
4	0.602	2.000	0.213	32.02	1.498
5	0.698	2.236	0.287	43.30	1.677
6	0.778	2.449	0.362	54.94	1.805
7	0.845	2.645	0.458	69.82	1.872
8	0.903	2.828	0.543	83.39	1.916
9	0.954	3.000	0.567	88.42	1.980
10	1	3.162	0.574	91.06	2.003

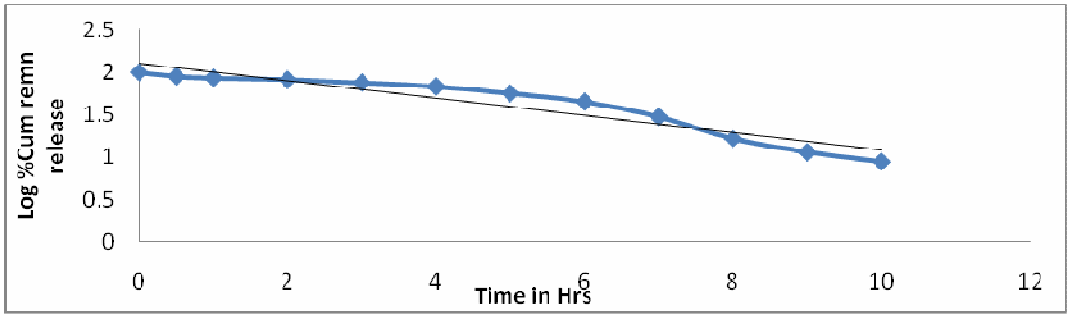
Graph No.27: Ex-vivo Dissolution profile for Formulation F3



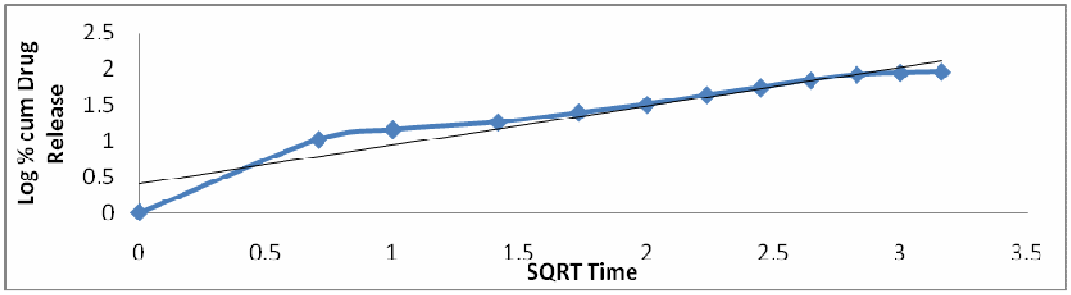
Graph. No.28: (a) Zero order Drug Release Kinetics for Formulation F3



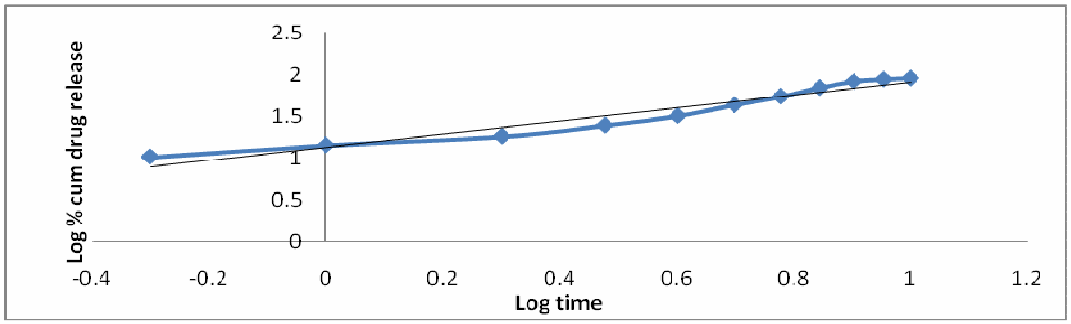
(b) First order Drug Release Kinetics for Formulation F3



(c) Higuchi's Drug Release Kinetics for Formulation F3



(D) Korsmeyer-Peppa's Drug Release Kinetics for Formulation F3



7.8 DRUG RELEASE KINETICS

Table No. 22: Drug release kinetics:

Batch	Zero order r^2 values	First order r^2 values	Higuchi r^2 values	Korsmeyer-Peppas r^2 values	'n' value
F1	0.984	0.721	0.966	0.997	0.793
F2	0.95	0.815	0.989	0.988	0.667
F3	**0.971**	**0.832**	**0.978**	**0.995**	**0.798**
F4	0.980	0.868	0.964	0.989	0.766
F5	0.990	0.794	0.944	0.988	0.897
F6	0.972	0.934	0.953	0.987	0.821
F7	0.994	0.826	0.939	0.985	0.822
F8	0.985	0.777	0.889	0.949	0.894
F9	0.980	0.785	0.955	0.973	0.745
F10	0.980	0.872	0.956	0.983	0.752

Table. No. 23: Model fitting for formulation F3

Formulation	Mathematical models				
	Zero order	First order	Higuchi model	Peppa's model	'n' value
F3	0.971	0.832	0.978	0.995	0.798

Table. No. 24: Stability studies after 90 days storage of selected formulation (F3) at Room temperature (RT) and 40^0c and 75%RH

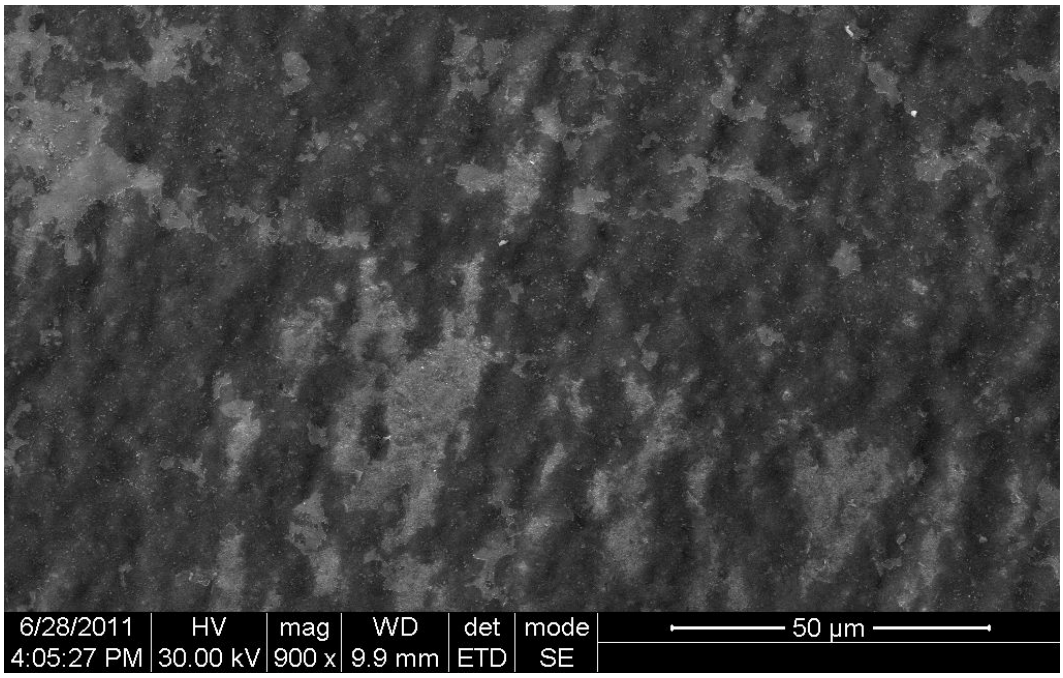
Storage conditions	Days	Bio adhesive strength	In-vitro residence time	Drug content (mgs)	Cum% drug release (10hrs)
Room temperature	30	182	421	3.70	99.41
	60	183	423	3.71	99.02
	90	185	425	3.65	98.67
At 40^0c and 75%RH	30	179	417	3.72	99.45
	60	177	420	3.69	99.08
	90	175	418	3.62	98.12

Inference:

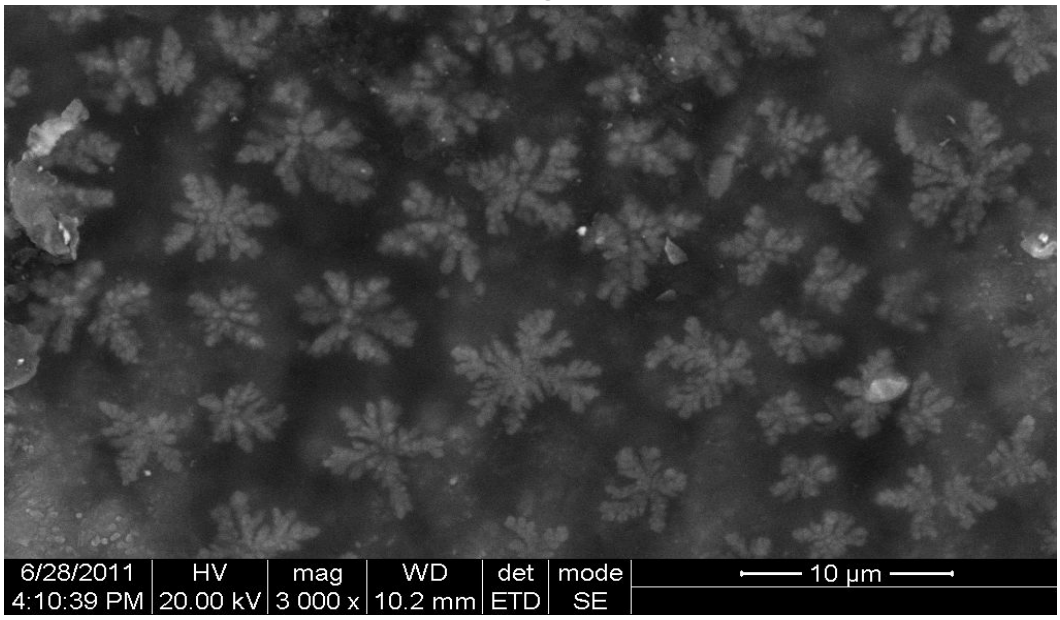
From the above data it was evident that there was no significant change in the physical and performance parameters of Dimenhydrinate buccal patches during the stability studies conducted at Room temperature and 40°C & 75%RH for 3 month period.

FIG.NO.29: SEM PHOTOGRAPH OF FORMULATION F5

A) SEM photograph of plain buccal patch



B) SEMphtograph of buccal patch with drug



6.2. DISCUSSION

Oral drug delivery system represents one of the frontier areas of controlled drug delivery system; such dosage forms are having a major advantage of patient compliance. A controlled release matrix dosage form is defined "as one for which the drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms.

Dimenhydrinate is H_1-antagonist used in the Treatment of nausea and vomiting caused by drug or motion sickness. The conventional doses release the entire drug in just few minutes and therefore the therapeutic concentrations are maintained for a short period of time generating a need for administration of another dose. Therefore a sustained release formulation of Dimenhydrinate which would release the drug over a long period of time is beneficial.

In the present work efforts have been made to develop the controlled release Muccoadhesive buccal patches of Dimenhydrinate prepared by solvent casting technique using HPMC E15, HEC, PVA and PVP in different ratios to produce the therapeutic dose is needed to be maintained for long time.

7.1 PREFORMULATION PARAMETERS:

7.1.1: Determination of λ_{max} of Dimenhydrinate:

On the basis of preliminary identification test it was concluded that the drug complied the preliminary identification. From the scanning of drug, it was concluded that the drug had λ_{max} of 276 nm, which was equal to 276 nm as reported. Also, an IR spectrum was concordant with the reference spectrum of Dimenhydrinate.

7.1.2: Preparation of standard calibration curve of Dimenhydrinate:

From the standard curve of Dimenhydrinate (Table No.7, Graph 6), it was observed that the drug obeys beer's law in concentration range of 1-10 μg/ml in Distilled water. The linear Regression equation generated was used for the calculation of amount of drug.

7.1.3: Determination of IR spectrum of Dimenhydrinate:

Physical mixture of drug and polymer was characterized by FT-IR spectral analysis for any physical as well as chemical alteration of the drug characteristics. From the results, it was concluded that there was no interference in the functional group as the principle peaks of the Dimenhydrinate were found to be unaltered in the drug-polymer physical mixture, indicating they were compatible chemically.

7.1.4: Drug excipient compatibility studies:

Drug-Excipient compatibility studies form an important part of Preformulation studies for the determination of interaction between drug and excipient. It is determined after storage of specific time period by using suitable analytical techniques and the results are indicating that there is no interaction between drug and excipients.

7.2 FORMULATION DESIGN:

7.2.1: Formulation of the controlled release mucoadhesive buccal patches of Dimenhydrinate:

Total 10 formulations of Muccoadhesive buccal patches were prepared with different polymers such as HPMC E15, HEC, PVA and PVP in different Ratios and proportions by Solvent casting technique. The prepared Muccoadhesive patches were then evaluated for various physico-chemical tests like thickness, folding endurance,

weight variation, water uptake, bioadhesive strength, drug content uniformity, surface p^H, Mechanical strength, Scanning electron microscopy (SEM), In-vitro release study, Invitro residence time, Ex-vivo drug release study, Stability study and Kinetic study.

EVALUATION PARAMETERS:

Physical properties:

Thickness of patch:

The thickness of the prepared buccal patches of each formulation was determined with in the range of 0.23- 0.26mm.

Folding endurance:

The folding endurance of each formulation was determined with in the range of 302 to 318. It revealed that good flexibility of patch.

Mechanical strength:

Three patches of each formulation were evaluated and mean values are recorded in table no.9.1. The values were found to be in the range of 5.28 to 12.94kg/mm^2. The values revealed that the patches were having good mechanical strength.

Water uptake study:

Water uptake of all buccal patches containing Dimenhydrinate is given in table no.9.1. The swelling of patch was changes with respect to polymer ratios. The values were found to be with in the range of 1.93 to 2.93.it was maximum for F3 i.e. 2.93. It is revealed that swelling nature of polymer.

Performance parameters:

Content uniformity of active ingredient:

Table no.9.2 shows the result of drug content uniformity in each formulation. Three replicates of each test were carried out. The mean drug content was found to be in the range of 3.68 to 3.8 for (each patch size 10mm diameter) the prepared buccal patch formulations. It is indicating the uniform distribution of drug in polymer matrix.

Measurement of bioadhesive strength:

An effective buccal mucosal device must maintain an intimate contact with mucus layer overlying the epithelial tissue. This parameter very important to successful utilization of these dosage forms. Hence in-vitro evaluation of buccal patches was carried out using porcine gastric mucosa. This gives the indirect measurement of bioadhesive strength in grams.

The maximum bioadhesive strength and force of adhesion was recorded for the formulation F3 and the values were 187.67 and 1.82 respectively.

The Invitro residence time was recorded and the values were changing with different ratios of polymers and the maximum for F3 about 490 mins.

Measurement of surface P^H :

They were found to be with in the range of 6.3 to 6.6 for all formulations and were almost with in the range of salivary p^H i.e. 6.2 to 7.4. There was no considerable difference in surface p^H of patches. It represents the better patient acceptability.

In vitro release study:

The in-vitro dissolution was studied in phosphate buffer p^H 6.8. The Invitro dissolution studies were carried out in triplicate and the results shown in the tables are mean of the replicate values. The Invitro released data obtained for patches F1 to F10 are tabulated in table no.10 to 19 respectively. The maximum release was observed in F3 formulation, it was up to 10 hours. The release is due to the uniform and proper mixing of drug and polymers which enables the drug to release in steady state manner.

Criteria for optimization:

The formulation F3 is optimized on the basis of Invitro drug release, swelling index, long Invitro residence time and good bioadhesive strength. The Ex-vivo release studies were performed by using 7.4 P^H saline phosphate buffer for formulation F3 by using porcine buccal mucosa as a model membrane and it was shown that good drug permeability across the membrane above 10 hours.

Stability study:

Stability studies of the prepared buccal patches were carried out, by storing formulations F3 at, room temperature and humidity and 40^0 C±2^0C/ 75%RH ± 5% RH in humidity control oven for ninety days. Stability studies were carried out to predict the degradation that may occur over prolonged periods of storage at various temperatures and humidity for formulations F3 over a period of 90 days. The results of the stability studies, which were conducted for 90 days, are shown in table no.24. The result obtained showed a slight decrease in, in vitro release of formulations F3 as

compared to the fresh formulations F3. The shelf life of the fabricated device was calculated based on these parameters.

Kinetic study:

To study the drug release kinetics, data obtained from In-Vitro drug release studies are plotted in various kinetic models. The curve fitting results of the release rate profile of the designed formulations gave an idea on the mechanism of drug release.

Based on the "n" values are ranging from 0.745-0.893 for all the formulations formulation, the drug release was found to follow Anomalous (non-Fickian) diffusion. This value indicates a coupling of the diffusion and erosion mechanism (Anomalous diffusion) and indicates that the drug release was controlled by more than one process. Also, the drug release mechanism was best explained by zero order, as the plots showed the highest linearity (r^2 = 0.971), as the drug release was best fitted in zero order kinetics, it indicated that the rate of drug release is concentration independent.

7. SUMMARY AND CONCLUSION

7.1 Summary:

Dimenhydrinate is a H_1 Antagonist; it is used in the treatment of vomiting caused by motion sickness.

As the conventional doses release the Dimenhydrinate in just few minutes and therefore the therapeutic concentrations are maintained for a short period of time generating a need for administration of another dose. Therefore an attempt was made to maintain the therapeutic concentration for longer period of time. This was achieved by developing controlled release drug delivery system.

These controlled release Muccoadhesive buccal patches mainly prepared for release of the drug for longer period of time i.e., 10 hours and utilizing the drug to full extent avoiding unnecessary frequency of dosing.

For the formulation of Muccoadhesive buccal patches HPMC E15, HEC, PVA and PVP were used as matrix forming agents. Other excipients used are Propylene glycol as a plasticizer. Fourier transform Infrared spectroscopy confirmed the absence of any drug/polymers/excipients interactions.

The Muccoadhesive buccal patches were prepared by solvent casting method using magnetic stirrer. The prepared controlled release Muccoadhesive buccal patches were evaluated for thickness, folding endurance, weight variation, water uptake, bioadhesive strength, drug content uniformity, surface p^H, Mechanical strength, Scanning electron microscopy (SEM), In-vitro release study, Invitro residence time, Ex-vivo drug release study, Stability study and Kinetic study.

Formulation F3 showed good Bioadhesive strength and a controlled drug release and also shown good result for all other parameters when compared with all other formulations. Hence formulation F3 is considered to be the optimized formulation. Stability studies were carried out for F3 formulation they had showed good stability when stored at accelerated stability state as per the ICH guideline and the values were with in a permissible limits.

It was observed that Formulations F3 retained the drug release up to 24 hrs. All formulations were subjected for four different models viz. Zero order, First order, Higuchi matrix and Peppas model equations and all the formulations best fit in to the Peppas model by giving the values of diffusional exponent (n) in the range of 0.6-0.9 that indicate the formulation had release the drug by diffusion followed by erosion mechanism.

It was revealed that polymer ratios had significant influence on drug release. Thus conclusion can be made that stable dosage form can be developed for Dimenhydrinate for controlled release by buccal patches.

7.2 CONCLUSION

In the present study, an attempt has been done to develop a novel muccoadhesive drug delivery system in the form of the buccal patches for the release of Dimenhydrinate in a bidirectional manner, to maintain constant therapeutic levels of the drug for long time.

Buccal formulations of Dimenhydrinate in the form of muccoadhesive patches were developed to a satisfactory level in term of drug release, bioadhesive strength, content uniformity, percentage water uptake, surface P^H, thickness and mechanical strength.

Although all buccal patches exhibited satisfactory results, best results were obtained with optimized formulation F3 containing HPMC and HEC in 1:3 ratios. Invitro dissolution studies of the optimized formulation showed that the percentage cumulative drug release about the release of Dimenhydrinate from the patches in the present work appeared to occur due to diffusion and erosion mechanism. The release pattern was found to be non-Fickian.

The above study concluded that the possibility of the making of mucoadhesive drug delivery system for Dimenhydrinate which will be more efficacious and acceptable than conventional drug delivery of Dimenhydrinate and also having satisfactory controlled release profile which may provide an increased therapeutic efficacy.

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